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INTRODUCTION TO GROWTH

Experience has shown that journals devoted to disciplines are useful. It has yet to be proven that a journal devoted to a fundamental property of nature regardless of the discipline used in its study would be similarly useful. Yet it would seem rational procedure to assemble between the covers of a single periodical all work, however diverse its procedure, which is aimed at evaluation of a common property.

Growth is a fundamental and common property of nature. Its course is governed by fundamental laws common to its expression where and whenever this is manifest. The workings of these laws are to be found in the growth of crystals as in the growth of populations; in the growth of intelligence as in the growth of a root; in the growth of yeast as in that of an elephant. Growth is growth wherever found. But growth is not single. It is multiple, the combined expression of developmental and incremental factors. Increase in cell number is as much growth as is increase in cell size. Increase in cellular specialization is as much growth as is increase in cellular segregation. The laws which govern proliferation, differentiation, organization, mass increment, and all or any other growth expression of common possession may be assumed to be the same for all growing objects regardless of their structural, functional, or other distinguished attributes.

To uncover these laws and to test them; to set forth the determining chemical, physical, and genetic participants in each; to expose the processes in terms of mathematics, statistics, chemical reaction and physical attribute; to state the significance of developmental function; to review the accomplishments of the past and proffer suggestions for the future, are one and all matters of interest to the student of growth.

To have a medium where such studies may meet is to provide a means whereby should come that integration through which understanding to usefullness is possible. Such is the basis and the purpose of the journal GROWTH.

To bring this principle from idea to action would seem to require a certain number of editors. For it is basic that every author has the right to expect his work will be passed on by one familiar with its substance. Therefore an attempt is here being made to distribute editorial responsibility among representatives of the major lines of approach to the general problem. This also makes available intereditorial appraisal where the material would seem to require review in more than one discipline.

It would seem that the primary editorial obligation is the forwarding rather than the obstruction of publication of scientific work. And it would seem that every author should have the right to expect prompt consideration and decision regarding his work. Though each editor of GROWTH quite naturally has the privilege of consulting with colleagues on and off the Editorial Board the fact is recognized that assumption of competency to pass judgment on a paper *after* it is published implies competency to pass on it *before*. The considered

application of this principle should do much to reduce delays occasioned by unnecessary shunting of sound papers from editor to editor.

Some day some one will write an analytical history of the growth of scientific publication in which will be traced the practices, origins, and factors which have produced the present system. A system where multiplicity of journals invites meagre subscription lists; where meagre subscription lists mean meagre financial support for the individual journal; where meagre financial support means restricted publication facilities; where restricted publication facilities means not only inadequate and delayed publication but also the starting of more journals to take care of the ever increasing number of papers; which means higher and higher subscription costs; thinner and thinner subscription lists; and so on and on until the spiral ends where only libraries subscribe and the individual worker has but hardy access to the work of others.

To cut it straight—it is necessary that the records of scientific work be published in adequate completeness; that they be published promptly on completion of the work; and that they be made easily available through wide dissemination. That these vital functions are not being expressed as they might be is obvious. There is but one solution. And this is to put the cost of publication of scientific work where it belongs and that is on the institutions sponsoring the work.

By so doing the institution rather than the editor determines the limits of adequate presentation. This is as it should be since the worker knows more about what he has done then any editor and no one can justly appraise the value of any given piece of work at the time of its presentation. By so doing publication is not held up either by the mass of previously accepted papers waiting their turn, nor by time wasted in peddling the report from one set of harassed editors to another. And by so doing the results become generally available in other than abstract form because subscription cost is restricted to that involved in wrapping, addressing, and mailing.

It should hardly be necessary to indicate that if this obviously advantageous and sensible system were generally put into effect it would be possible for the number of journals to be reduced and for every worker to subscribe not only to the journal carrying work in his own field but also to those of allied interests. In so doing the sphere of observation, vision, and usefulness of the individual worker could be immeasurably enlarged. The inevitable integration could not but foster scientific solidity.

These then are the principles which GROWTH will attempt to express. In so doing it expects to encounter all the circumstances incident to such pioneering.

FREDERICK S. HAMMETT

AN IMPROVED TECHNIQUE FOR MEASURING HEAD FEATURES

By
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(*Received November 19, 1936*)

A measuring technique is described which involves the holding of the head in a fixed position, the measurement of features by projection from a vertical wall, the checking of projected measurements by direct measurement.

STATEMENT OF PROBLEM

The accurate measurement of the small facial features from infancy to maturity requires, first, an appropriate technique and, secondly, a checking of the measurements. Experience with repeated measurements on the same child have shown the important error involved in single measurements. (Davenport, Steggerda and Drager, 1934.)

METHODS

The ordinary method of measuring heights of facial features is by means of sliding calipers, length and breadth of the head by compass calipers, head height by special calipers such as those of Matiegka, Prague, and nose depth and salient by reversed sliding calipers. I have added a useful technique involving reference to a vertical plane.

The subject is seated on a box about 18 inches in height with his back to a wall (Fig. 1), his head being placed exactly against a vertical line which is 15 feet from a corner of the room. On the opposite wall (about 12 feet away) is placed a vertical rod (*v.r.*), perforated with holes about 5 mm. in diameter at intervals of 2 cm. marked with heights in centimeters starting at 0 at the floor. This rod is held precisely in place against the vertical wall, 15 feet removed from the corner of the room on its side. A plane mirror (*m*), about 1.5 cm. wide and 8 cm. long, is placed on a mortar board support, of which the handle forms a pin that fits closely into the above mentioned holes. When so fitted the mirror is parallel to the wall and is placed with its long axis strictly horizontal.

The subject is placed with the Frankfort horizontal (*F.h.*) in position, with the occiput against the wall and the sagittal plane perpendicular to the wall. This perpendicularity can be checked by measurement from the wall to the tragion on right and left sides. The height of the pupil from the floor is measured with the anthropometer and the mirror set as nearly as possible at the same level across the room (Fig. 1). The subject can now see his eyes in the mirror, and can do so at no other position of the mirror. The subject is told to keep the occiput in contact with the wall, keep looking at his eyes in the mirror, and not to move his head after it has been placed in the desired position, perpendicular to the wall.

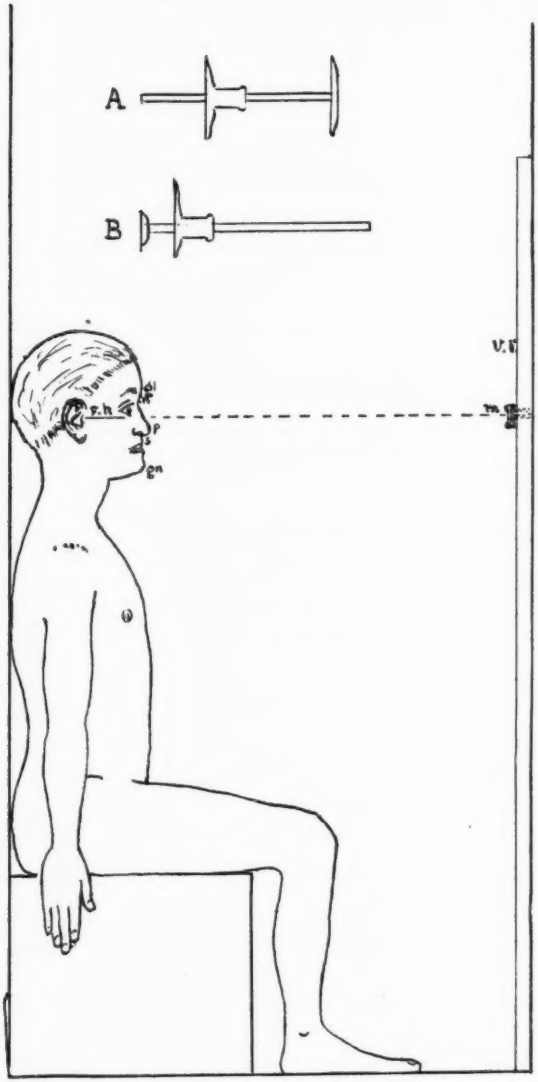

FIG. 1. Outline of a child in position for measurements of the head and facial features, *F.h.* Frankfort horizontal; *m*, mirror; *v.r.* vertical rod; *gl*, glabella; *n*, nasion; *p*, pronasion; *s*, subnasale; *g*, gnathion. A, sliding calipers used in direct measurement of facial features. B, depth measurer for measuring projections of head and facial features from the wall.

Owing to the fact that the angles of incidence and reflection in the mirror are equal, any deviation of the pupil and mirror from the same horizontal plane will show to the subject a part of the head above or below the eyes. This adjustment is very delicate.

The head and facial features are now measured by projections from the vertical wall and in doing so the "depth measurer" (Fig. 1, B) made by Rickenbach and Sohn, Zürich, is found very useful. The distances of tragion on right and left side, the distances of the bottom of the orbit on both sides, the distances of glabella (*gl*), nasion (*n*), pronasion (*p*), subnasale (*s*) hinder insertion of ala, and gnathion (*g*) are all determined.

To check these horizontal measurements one uses the sliding calipers of Rickenbach with reversed end (Fig. 1, A). The nose depth is measured on the two sides of the nose and the readings averaged. The nose salient is measured from subnasale to pronasion (*s* to *p*). This last distance should agree with the difference of the horizontal measurement of pronasion and subnasale. If it does not (and it is remarkable how often the agreement will not be exact) then the horizontal measurements and the direct measurements must be repeated until they agree to not over a millimeter.

In the case of infants who are measured on the measuring board in a horizontal position, the Frankfort horizontal must be strictly vertical and the depth measurers used with the measuring board as a base. These projection measurements of the nose can be checked by direct measurement with the reversed sliding calipers. After about one and a half years of age the head of the small child can be measured from the vertical wall, as in the case of older children.

RESULTS

The course of changes of proportions in head and face will be considered in another paper. Suffice it to say that the head is obviously undergoing marked changes in proportion from infancy to maturity as has already been hinted at in the literature. The face, which undergoes such profound changes during intrauterine life, continues to show changes in proportion of its features from birth to the third or fourth decade of life.

CONCLUSION

The ordinary method of measuring the head and face without a plane of reference and without checking gives rise to results so unreliable that they are inadequate for the study of developmental changes. Just as craniologists have used planes of reference so must students of growth of parts in the living use such planes where possible. Of course it is recognized that in studies in primitive regions where there are no adequate walls the above described method would be difficult to apply. However, by using a board and having the subject assume the horizontal position the above technique can be approximated too.

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ON THE MOTION OF GROWTH

XVII. THEORETICAL FOUNDATIONS*

By

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(*Received December 6, 1936*)

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* Delivered in substance at the Physics Colloquium, Case School of Applied Science, Cleveland, December 17, 1935. and in part before the National Academy of Sciences, November 20, 1934.

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INTRODUCTION

In previous papers of this series, emphasis has been mainly placed on various results that have been obtained by treating growth in living things as a mode of generalized motion. Preference has heretofore been given to the results themselves, partly because they are bound to be of more immediate interest, but also because it has not been possible, until now, to present a reasonably full account of the theoretical foundations of this theme.

The view that growth be looked upon and treated as a mode of motion has proved useful and fruitful. It has helped, in ways not altogether easily described, to develop what now seems to be the most important single result of these studies: a set of equations by which the heat production of growing organisms is expressed directly in terms of the corresponding rate of growth. As a consequence it is now possible to understand why maxima, or even indeed minima, appear in certain curves of heat output in various organisms at one stage or another of their life careers, and why they occur at the points they do.

Take, as an example, the curve for the daily rate of heat production in the human case. Study of the matter by the present methods has demonstrated the existence of an interesting and important oscillation in this curve between one and four years of postnatal life. But the oscillatory character of heat output during that interval cannot be discerned even in the best of modern data on the subject, owing, of course, to the unavoidable scatter in the observations. This, in fact, is quite sufficient to obscure, and thus to prevent the detection of a maximum between one and two years, or again, the recognition of a minimum between three and four years by experimental measurements alone. It has, moreover, proved possible, in further studies, to correlate this peculiar trend of heat output during the transition between infancy and adolescence with the conspicuously frequent clinical phenomenon of pre-school anorexia, and thereby to institute principles of sound therapeutic treatment and care.

Since similar oscillations have also been found in the heat curves of other organisms, by treating heat output as a function of the rate of growth, we may learn to anticipate the existence of peaks and troughs where these have not as

yet been found or looked for; or, finally, to understand why still other examples do not display such oscillatory trends at all.

All of these are crucial cases, yet they cannot be accounted for by the body surface law. The tenets of this law, though widely quoted and relied upon as explaining the high rates of heat output characteristic of young subjects, which stand out in strong contrast to the low rates found among homologous adult forms, break down when attempts are made to apply them to the whole life episode; they fail to hold especially during those intervals that precede and include the peaks of heat production. The resulting contradiction can be avoided, however, by considering heat production, as we do here, to be an explicit function of the rate of growth.

Let us grant, then, that the foregoing results, to mention but these, are almost unrecognizably far removed from the original postulate that growth can be conveniently referred to as a mode of motion. It would be well, accordingly, to give some justification for this view.

Considering, to begin with, that the results just mentioned are already established, we may at once recognize that there are undoubtedly other methods by which equations for growth, and indeed also expressions connecting heat output with growth, could be obtained. If these analyses could proceed without the slightest reference to the idea of generalized motion, it would, of course, be quite misleading to mention "motion" in them. Their development, then, could not depend at all upon, and could not be traced to, the equations of Lagrange. But investigations of this kind would also be required to treat the problem of growth without employing the concept of energy, at least in any way in which energy would enter in the so-called differential form. Yet, to treat the subject of growth and at the same time to avoid every reference to energy is obviously impossible, provided we desire, as here, to take account not only of the purely kinematical aspects of growth, but also of the transformations of energy that accompany all real growth. The problem, moreover, would not be solved by calling upon Hamilton's principle, because this, too, would lead to the use of Lagrange's equations. Since the latter have been traditionally referred to as "equations of generalized motion," it is hardly possible to escape the term "motion" in the present investigation at the point where we assume, for reasons fully explained, that these equations may logically be introduced into the analysis of growth. This being so, it will be proper to speak of growth in motion even before that point is reached.

Perhaps the greatest difficulty tending to prevent a ready understanding, and thus an easy acceptance, of the present concept concerning the motion of growth can be traced to the almost universal impression that *motion* signifies simply and solely mechanical motion, and hence, nothing but the phenomena associated with the displacement of a body in space. Whoever seeks to restrict the idea of motion to this extent parts company with Plato among the ancients—who himself classified growth as the sixth in a series of ten kinds of motion—as well as with Lagrange and Maxwell of more modern times. For motion, in the general sense, implies nothing more than *change*, and hence, in the familiar and obviously most common case, that of mechanics, quite specifically, *change of position*

(in space). In mechanics, moreover, the term motion ordinarily refers most simply to a body that is not at rest.

Thus, in employing the term motion in the equally special case of growth, we recognize, though not obliged to do so, that motion here would refer to the whole set of phenomena associated with the *changes in size* which growing organisms undergo. We can, in addition, readily distinguish between organisms whose size is unchanging, that is, between the adults of a species and those whose size is undergoing unmistakable change, the infants of the species, and we may naturally refer to the latter as being in the motion of growth in comparison with the former who are clearly at rest with respect to growth.

Consider, as a further illustration of the point, two culture tubes: the one "old" and stagnant in its products—the other, "alive" with rapid, luxuriant, and uninterrupted reduplication. Familiarity with these, or indeed with comparable examples, soon helps to establish an intelligible perception of what the phrase "motion of growth" is capable of implying, much in the way that sensory perception likewise lies at the base of our ordinary understanding of pure mechanical motion.

Beyond this, we need hardly go at present, for the real meaning of either type of motion is surely too remote a philosophical question to be the subject of further inquiry here. The concept has proved useful, and it affords a convenient manner of speaking. This becomes more evident as we continue to investigate growth by the present methods. Those, to whom the term motion seems inappropriate, in spite of what has now been said, will find that a variety of other and less specific phrases may be substituted throughout the present text without altering the original meaning of any passage; they will be obliged, accordingly, to avoid its mention in the established phrase, "equations of generalized motion," and, in the modernistic fashion, to call these simply "Lagrange's equations" or, perhaps, his "equations for non-conservative systems."

With these initial views in mind, we shall proceed to give a connected outline of the present theory of growth which, though largely pursued by mathematical methods, is definitely founded upon direct observation and experiment. The analysis is even now sufficiently well advanced to the stage where continued repetition of observations already abundantly available cannot prove as helpful in a study of this theory as new experiments specially designed to test its implications. It is therefore proposed, though dealing primarily with the theoretical aspects of the subject, to keep within full view what actual experiment has already corroborated. This approach will help to suggest many further experiments in the closely allied fields of growth, nutrition and metabolism.

After a few preliminary remarks whose purpose it is to outline the main concepts we shall use and to describe the chief characteristics of growth in simple and in more complicated organisms, we shall define the quantity q in terms of which growth is to be measured. With this established, we shall consider the curve of a very general case of growth and discuss its significant geometrical features in the section on the kinematics of growth. But the main purpose of the present paper will be to show that growth belongs to the dynamical phenomena of nature and to indicate various applications of this result.

PRELIMINARY REMARKS*

Organisms.—Living things are composed of one or more cells and are, accordingly, classified as unicellular or multicellular organisms. The individual cells of the former, in suitable surroundings, are complete in themselves; they are capable of maintaining a separate and independent existence; and, for a given species, they are substantially alike. The cells of the latter, on the contrary, are not, in general, alike; for, having undergone what is called differentiation of type, they become congregated into tissues of differing structure and physiological function. Thus, multicellular organisms depend for their existence upon the cooperative action of the various complex tissues out of which the body of such animals and plants is formed.

Development: Growth and Differentiation.—Organisms of either class are endowed, from the moment of their inception, with the property of development. This, in turn, depends primarily upon an adjustment between growth on the one hand and differentiation of the resulting cells and tissues on the other hand. Growth is accomplished fundamentally by the process of cellular self-multiplication and it is, therefore, basically concerned with change in size, that is, with change in cell number, length, area, volume, or mass. Differentiation, meanwhile, effects a change in structure.

From the phylogenetic as well as from the ontogenetic point of view, growth is certainly the more primitive attribute, differentiation the more recent as well as the more highly specialized acquisition of organisms. But, in contributing to the development of a single being, growth and differentiation act in conjunction. This implies organization. The living result, an organism, thus owes an indeterminate share of its final arrangement to each of these processes; yet we may say that it attains size by virtue of growth, and architectural style by the concomitant process of differentiation.

Growth is the more accessible of these two phenomena and it is certainly more easily subject to measurement, even if only indirectly so.

The changes in size associated with growth take place in time; this, however, is but one of the characteristics that make it convenient to look upon growth as a *mode of motion*.

Energy for, and Work of, Growth.—Like other forms of motion,† growth demands expenditure of energy. Thus, development in general, and growth in particular, together imply, on the part of the organism, not only access to suitable sources of energy, but also the capacity of converting and of utilizing these sources. It becomes necessary, accordingly, to study the intrinsic relationships between change in size and the accompanying energy transactions including the work which these changes entail, and hence to investigate not simply growth alone, but the work of growth as well.

* For details on the biological properties of organisms and on the concepts of development, growth, and differentiation, reference must be made to larger treatises, e.g., Bertalanffy (1932), Child (1915), de Beer (1924), Fauré-Fremiet (1925), Huxley and de Beer (1934), Minot (1908), Needham (1931), Thompson (1917), and E. B. Wilson (1925).

† See Introduction for explanation of motion.

Somewhat beyond this, at least for the present, is a study of the real connections between nutrition, or the physiological properties of food, and growth. The ultimate objective is to learn whether "normal" or "abnormal" growth can be placed under control, and if so, how this may be accomplished.

We shall now review some fundamental aspects of the problem.

Systems of Growth: Source, Cells, Environment.—The motion of growth takes place in a *system* composed of three main parts: (1) living cells capable of reproduction, in the form of unicellular or multicellular *organisms*; (2) a suitable *source* of energy; and (3) an *environment* which permits growth.

General Characteristics of Simple and Complex Systems.—An ordinary *pure* culture of bacteria, consisting of similar organisms, is typical of the simpler systems. In this, the *source* of energy, the *cells*, and the *environment* are always in immediate physical contact, and the system in question is isolated from other systems. Among such homogeneous populations mutual effects are evidently identical. A mixed culture of bacteria, accordingly, is more complex than this and the influence of cells of one type upon those of another will not in general be alike.

Systems which support multicellular aggregates are still more complex. The *source* of energy, for example, may consist of several parts in greater or lesser proximity to, and even within, the body of the organism. Special devices then exist whereby inner sources may be replenished from some main external source. The *environment* of these systems is likewise more complicated. It consists of the *immediate environment* of cells and tissues, and of the *surrounding environment* of the whole organized aggregate. Such systems are not in general isolated from one another. It is evident that mutual relationships among intermingled systems ultimately become extremely intricate. We select only the more accessible features of growth in these systems for further discussion.

Growth in the *organism* implies the active participation of the two remaining elements of a system, namely, of the *source* and the *environment*, at every stage of the process. The chief events are well illustrated in a culture of unicellular organisms. It is noteworthy that these may be profitably reviewed without any explicit quantitative definition of growth.

The Chief Events Accompanying Growth.—Let growth become initiated in a simple system. This, clearly, can only be accomplished by the introduction of at least one cell that is capable of reproduction into a culture medium which provides a suitable source of energy, and propitious *immediate* surroundings.

The appearance of newly produced daughter cells is sufficient to establish the existence of growth.

Once initiated, growth tends to remain in motion.* It will do so provided all important conditions can be kept the same. Ideally, the motion will consist, since daughter cells are coming regularly into being, of a continuous† and steady

* See section on the inertia of growth, p. 22.

† From the restricted morphological point of view, integral values alone could be used to represent cell number and the result by which a single mother cell gives rise to two daughter cells would necessarily be a discontinuous *event*. Here, however, we are taking the view that the changes within the cell which lead to, and include, scission are continuous, and we may accordingly admit fractional as well as integral values of number or mass.

change in cell number. The resulting population will be uniformly distributed within the culture, the concentration of cells per unit volume remaining below the level at which mutual effects become operative. This conforms to the original assumption that constant conditions remain in force.

The significant event in such a system is change in population number and this has been achieved by the biological process of cellular self-multiplication.

On the practical side, however, we recognize that the source of energy has meanwhile been drawn upon, the cells certainly not having been produced *ex nihilo*. Unless replenished, the quantity of energy at the source will diminish. But this will ultimately alter one of the important original conditions of ideal growth and we shall necessarily expect a change in the motion of growth.

Further, cell surroundings in a system of finite dimensions will also have been altered, the changes being associated, in particular, with the ultimately greater concentration of the cells themselves, the accumulation of by-products, and with the effect of cell upon cell. We shall again expect that the original motion of uniform cell production must necessarily become altered.

Similar events take place in systems supporting the growth of multicellular aggregates. The evident specialization of tissues and their intricate organization into a single being must not be allowed to conceal the real issue in the problem. For here again, cellular self-multiplication is basic; cellular and tissue differentiation, if not unimportant, are certainly subsidiary. There is, moreover, an additional complication: the extension of the developing cell aggregate within a suitably chosen three dimensional frame of reference. While this is often symmetrical with respect to one or more of the individual axes, it is not, in general, equal in all directions; it is accompanied by, and indeed leads to, change in body shape. We cannot, in such a population, continue to deal directly, except as a basic notion, with cell number.

Measures of Size in Multicellular Organisms.—In place of the inaccessible attribute of cell number, we have at our disposal length, and the two functions of length, area and volume, as well as the attribute of mass, in which population size may be expressed. To overcome the objection that a complete analysis of change in size would thus require consideration of a multifold infinity of data, let it be recalled that changes in length or in shape, for example, are not entirely independent of changes in mass. This suggests that we have merely to select a single *independent* attribute in terms of which changes in size may be appropriately and most conveniently expressed. Changes in the remaining visible attributes of size are thus suppressed, as it were, but no more so than changes in body composition and in organization, or than the equally important changes that must be presumed to accompany the actual molecular construction of protoplasm. For the present, then, we shall confine our discussion of growth in multicellular forms to those examples, and there are many of them, for which mass itself can serve as a suitable measure of size. We thus come alternatively to associate growth, as Julian Huxley (1932) does, with "self-multiplication of substance;" the identity of the cells, like that of the individual particles in the organism, is submerged in the attribute of living substance.

Systems of One and of More Than One Degree of Freedom.—A system will be considered to have one degree of freedom with respect to growth when its cellular population can be represented by a single variable. Thus, a pure culture of bacteria is an example of a system in which growth may be said to have one degree of freedom. A mixed culture containing n varieties of unicellular organisms will have n degrees of freedom, since the several cell types are independent,* and n sets of data will be required to specify growth in such a culture.

In the absence of methods by which these changes could be individually measured, we should be obliged to deal with the population as a whole or else to drop the matter entirely.

But a multicellular form may be treated as a whole without incurring the same objections that could be raised against this procedure in the case of mixed cultures, because such an organism acts as a biological unit, and its component cells or cell types, at least in health, are subservient to the organization it represents, and are consequently not truly independent. In fact the development of a multicellular organism implies the existence of certain relations, not necessarily invariable, between the growth of its several tissues or parts. We have no knowledge of these relations but we do not require information such as this to treat the growth of a multicellular organism as a whole. Thus the growth of a single multicellular organism expressed in terms of a single attribute of size will be considered to have one degree of freedom.

Finally, systems with two or more multicellular organisms competing for energy from a common source will possess a corresponding multiplicity of freedom.

To sum up, we may say that the central event of growth is cellular self-multiplication and that this is accompanied by a change in population number or, more accessibly, in a multicellular organism, by a change in its size. We then deal simply with "self-multiplication," and the conspicuous differences between unicellular and multicellular organisms assume quite subordinate importance. If they are to influence growth at all they must act, as all other agents are likewise considered to do, upon the apparatus of cellular multiplication itself, upon the source of energy, or lastly upon the environment of native cells and tissues.

We proceed, accordingly, to express the quantity of self-multiplication, that is, of growth, explicitly in terms of size.

THE QUANTITY OF GROWTH q

Definition of q.—If z_0 be the initial, and z some subsequent value of population size in a system which has thereby undergone a quantity of growth q, it is obvious, from what has been said, that the difference $(z-z_0)$ cannot possibly represent the quantity of growth in question, or, in symbols, that

$$(z - z_0) \not\equiv q, \tag{1}$$

for $(z-z_0)$ represents only what can be called *gain* or *loss* in size according as $z \gtrless z_0$. It is readily understood that the difference $(z-z_0)$ does not express the

* Independence does not exclude the possible existence of mutual effects.

real meaning of growth if we recall that growth is achieved, in essence, by the process, described in the wholly figurative phrase "of cellular self-multiplication." The crux of the matter lies in the word "self," for the pertinent event in growth is a change in size relative to the amount of tissue that is generating, or is responsible for the generation of, the quantity in question.

We proceed therefore as follows. First we note that the z_0 cells initially introduced into the system correspond to some value of growth, say q_0, which has been accomplished in the past history of z_0, since the z_0 cells have not been produced out of nothing, and hence not without some previous growth q_0. Then, "self-multiplication" means that the further change in growth Δq accomplished by the change in size $[(z_0+\Delta z)-z_0]$ is, in fact, $\Delta z/z_0$. If now, the interval (z_0, z) be divided into n parts by the points $z_0, z_1, z_2, \cdots, z_{n-1}, z$, the approximate quantity of growth will be

$$\sum_{i=0}^{i=n-1} \frac{\Delta z_i}{z_i}, \qquad \Delta z_i = (z_{i+1} - z_i) \tag{2}$$

that is, the sum of the elementary changes $(\Delta z_i/z_i)$ in the n subintervals. Then the true quantity of growth q, that is, the *change in size per unit size* which the organism has undergone in experiencing the change $z_0 \rightarrow z$, will be given uniquely by,

$$q = \lim_{\substack{n\to\infty \\ \Delta z_i \to 0}} \sum_{i=0}^{i=n-1} \frac{\Delta z_i}{z_i}, \tag{3}$$

since $z>0$ and continuous* in the interval (z_0, z). We have, therefore, by the fundamental theorem of integral calculus,

$$q = \int_{z_0}^{z} \frac{dz}{z} = \log_e \frac{z}{z_0}, \tag{4}$$

[q]

which gives the quantity of growth corresponding to any change in size, $z_0 \rightarrow z$, where z_0 is fixed to suit initial conditions.

On physical grounds size z is positive, and is to be taken as a single-valued continuous function of the time t, throughout the interval $0<t<\infty$, with continuous derivatives of at least the first and second orders. Then q and its corresponding derivatives are likewise continuous functions of time over the same interval. For $t>t_0$, t_0 being the value of t at any arbitrary origin, it is usual in ordinary cases to have $z>z_0\geqq 1$, whence $q\geqq 0$. But values of z such that $0<z\leqq 1$, or $z\lessgtr z_0$, with the corresponding values of q, are not excluded.

Dimensions of q.—The dimensions of z depend on the unit in which size is measured. Thus, for cell number, we have $[N]$; for the various functions of length, $[L]$, $[L^2]$, and $[L^3]$; and for mass, simply $[M]$. The dimensions of q, on the other hand, are those of a pure number, but it is useful to designate relationships otherwise suppressed (if q is treated as merely of zero dimensions) by a

* See footnote on continuity, p. 11.

notation such as [cell·cell^{-1}], [gram·gram^{-1}], etc., or more shortly by [q_c], [q_g], etc., respectively, or, finally, without the accompanying subscripts where the context is clear.

THE KINEMATICS OF GROWTH

A General Curve of Growth.—Consider now, the curve $q=\phi(t)$ in Figure 1, which illustrates the character of the changes in a very general case of growth with one degree of freedom.* The quantity of growth which a system possesses

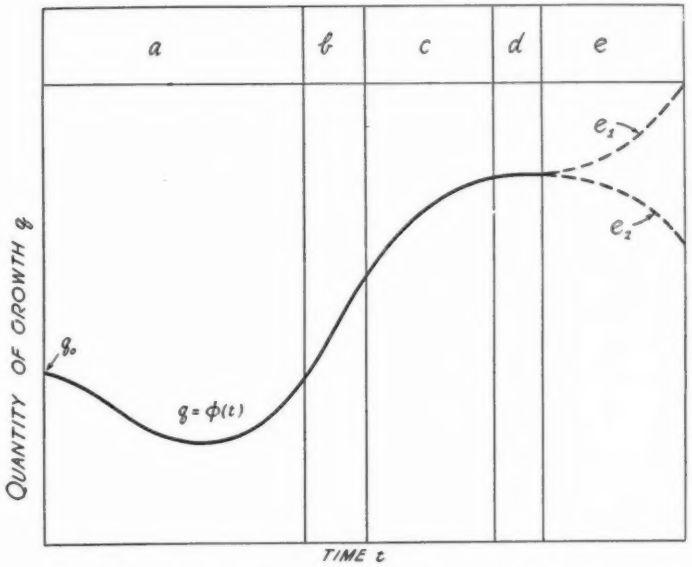

FIG. 1. The curve illustrates the general character of the change in the quantity of growth q as a function of time t, for example, in the case of one multicellular organism or of the *viable* population of similar unicellular organisms. The oscillations in q take place about a level of equilibrium, $q_f \gtreqless q_0$ fixed for any particular case by the physical circumstances of growth, but in general, not coincident with the value $q_0=0$. The vertical lines demarcate what are usually referred to as "phases" of growth: (*a*) Lag phase, (*b*) Logarithmic phase, (*c*) Phase of retardation, (*d*) Upper stationary phase. The alternative types of change (e_1) and (e_2) illustrate the potentially unlimited oscillation in q which ultimately degenerates, in practice, into an asymptotic approach, either from below or from above, to some stationary level of equilibrium q_f.

at any time t_r is q_r; but the motion of growth which the system has experienced throughout any interval δt is represented in that interval by the nature and extent of the corresponding displacement δq of a point on the curve with respect to the coordinate axes q and t.

* Growth of one multicellular organism or of the *viable* (not total) population of similar unicellular organisms. (See G. S. Wilson, 1922, and Graham-Smith, 1920–21.) *Cf.* p. 13.

A study of the graphical properties of such curves, without any reference to the possible agencies that act to produce growth, forms the branch of this entire subject which we shall call the *Kinematics of Growth*. We cannot treat it fully here, preferring to place the greater emphasis upon a study of the *Dynamics of Growth*, but some preliminary attention to the general nature of growth curves themselves is a necessary step toward the latter objective, and we shall, accordingly, give the main facts as briefly as possible.

"Phases" of Growth.—It has long served the purposes, and thus become the custom (see Buchanan, 1918), to subdivide a growth curve* along the time axis into several portions called "phases," similar to those shown in Figure 1. We shall retain this term, and specify as is usual (*a*) Lag phase, (*b*) Logarithmic phase, (*c*) Phase of retardation, (*d*) Stationary phase, and to these we shall add the alternative element (*e*), with Phase of restoration (e_1) or of decline (e_2).

In the more familiar examples, growth is originated at some point in (*a*), (*b*) or (*c*); it progresses to the right and terminates as in (*d*). There are, however, conspicuous and important cases in which growth does not draw to a close in (*d*); it proceeds, instead, with continuous transitions along either of the two branches in (*e*), each of which obviously possesses characteristics that belong to segments (*a*) and (*b*). Succeeding its entrance upon (e_1), growth is known to undergo a repetition of the oscillatory events between (*a*) and (*d*); similar changes may take place even after entering upon (e_2). Ultimately, degeneration of such potentially unlimited oscillation sets in, and the final stages consist of an asymptotic approach, either from below or from above, to some stationary level, $q_f \gtrless q_0$.

We see, then, that the trend of growth as represented by the graph $q = \phi(t)$ is in general highly complicated; for the changes in q are not usually equal in equal times nor do they always take place in the same direction.

Behavior of Systems; Curvature; The Function Φ.—It is clear that the state of the system in respect of the motion of growth, at any point, say t_r, is not to be defined simply by a knowledge of the position, q_r, which the system has reached at t_r. For, in being interested in the motion of growth, we are basically concerned with the mode of approach to, as well as away from, the point q_r, and hence in the trend of the curve in a neighborhood of q_r. The problem obviously calls, among other things, for a knowledge of the curvature at q_r, and since this, in turn, involves not only $\dot{q}_r$ but $\ddot{q}_r$ as well (where the dots refer to the first and second derivatives with respect to time), the behavior of the system at t_r, both with regard to its position and to the character of its motion, will depend on all of the quantities, q, $\dot{q}$, $\ddot{q}$, and t, at least, and it will be represented, if derivatives of higher order be ignored, by the equation,

$$\Phi(q, \dot{q}, \ddot{q}; t) = 0. \tag{5}$$

* It may be recalled that the terms "growth" and "growth curve" have been widely applied to curves that show simply cumulative increments in z, that is, to curves of $z = \epsilon^q = \epsilon^{\phi(t)}$. In accordance with the definition of q in equation (4), the term growth curve will here refer only to curves displaying the trend of q. It is again important to note that q for unicellular populations will be understood to refer to the viable rather than to the total population.

An approximate estimate of the behavior of the system may be obtained if three positions on the curve including the point in question are given. A more exact determination of the whole motion at any point will depend, however, upon the solution of equation (5) which, on this account, is to be called the equation of motion.

We understand from (5) that q is the dependent variable and t the independent variable in a case of growth with one degree of freedom. Thus, in any single system, $\dot{q}$ and $\ddot{q}$ will be defined since q is defined by $q=\phi(t)$. But, we may also interpret (5) to mean, since we have to consider all possible cases, that any q is consistent with any value of $\dot{q}$, $\ddot{q}$, at any t, a procedure which amounts, in this sense, to our regarding q, $\dot{q}$ and $\ddot{q}$ as independently variable. But again, so far as the conditions in any one system, subsequent to some initial value of t, say t_0, are concerned, the relationships between the quantities mentioned above are by no means haphazard, the general characteristics of the motion being represented by the graph $q=\phi(t)$, in Figure 1.

States of Growth; Symbolic Expressions.—The essential behavior of a system at any instant may thus be denoted by a suitable choice of values for the variables in the symbol $[q, \dot{q}, \ddot{q}; t]$, as, for example, during an instant of the logarithmic phase (b, Fig. 1) by $[q>0, \dot{q}>0, \ddot{q}=0; t_{(b)}]$. This notation, or slight modifications of it, will henceforth be used more explicitly to describe the state of a system undergoing growth; it has the advantage of drawing direct attention to the important features of the problem, and it avoids much of the kinematical uncertainty attached to the less precise names for the various phases already designated in the legend of Figure 1.

Next, it is clear that if (5) can be solved explicitly for q in terms of t, ϕ will be determined. We have therefore to determine Φ. A suitable form for Φ could be obtained from purely kinematical considerations, if this were, in truth, necessary and likely to be of indispensable help.

The problem of growth in motion, however, is more predominantly one in another branch of the subject, appropriately called, as we shall see, the *Dynamics of Growth*, within the province of which it will be to study those agencies that initiate, maintain, and, in general, control the motion of growth.

THE DYNAMICS OF GROWTH

Actions; Properties of Systems.—It is reasonable to suppose that the various events most simply displayed in, and represented by, the curve $q=\phi(t)$ are the result of organized activity on the part of source, cells, and environment; and, further, that such activity depends entirely upon a number of fundamental properties of those systems that support and manifest the motion of growth. We are also at liberty to suppose that such properties are, in general, functions of the quantity of growth q, or of its derivatives, and of the time t; in particular, cases must arise in which these properties could be distinguished and recognized. It remains, therefore, to find their connections with the motion of growth; and this, again, specifically calls for a determination of Φ.

We shall, accordingly, require additional information on the phenomena displayed by *growth in actual motion*. Before proceeding, however, to compile this, we shall anticipate the main results that will lead to Φ.

Methods of Analysis and Results.—The evidence shortly to be brought forward will show that the systems of growth we are now considering are in reality dynamical systems belonging to that group of other natural systems which have the following attributes in common.* Thus, for example, it will become plain that systems of growth are *nonconservative* in the purely dynamical sense. They are, in particular, of the nonconservative type, which manifests (*i*) *dissipative* as well as other reactions of a nonconservative character. They will be found, in addition, to possess the general property of *inertia*, that is, of *growth inertia*; as a counterpart of this (*ii*) a portion at least of their energy will be the *kinetic energy of growth* in motion. Another part of their energy will be seen to arise, not out of the motion of growth directly, but rather (*iii*) out of *positional properties* associated with the existence of a quantity of growth q in a neighborhood of equilibrium. These reactions will be found to balance (*iv*) the action of the source of energy itself.

The results just mentioned are to be obtained by applying the methods of classical mechanics, in particular the method of Lagrange, to the present problem. His equations will be modified to suit the case of growth and their solution will give Φ. What will thus have been gained on the dynamical side will finally be correlated and checked, not only against the kinematic facts that have already been presented but also against an array of actual data that have been collected by many investigators from direct observation and experiment.

We shall now consider various phenomena displayed by growth in motion in order to prepare for the application of the methods just mentioned. Taking up first those related to the property of heat production, we shall see that heat generated by growth itself accounts for only a portion of the heat that is actually liberated by growing organisms.

The Property of Heat Production

The Composite Nature of Heat Output; Heat of Maintenance; Heat of Growth.—To begin with, it is commonly known (*i*) that organisms in their capacity as living things, whether "growing" or not, produce and liberate heat. Now the process of simple biological existence (life), as distinguished from the process of growth, does not depend on change in size; in fact, simple existence may be construed as that state in which $\dot{q}$, along with higher derivatives, and hence, the motion of growth, vanishes. Thus, heat liberated by an organism in the state of simple existence $[q>0,\ \dot{q}=0,\ \ddot{q}=0]$ is *dissipative* not in the dynamical or motional sense, since $\dot{q}=\ddot{q}=0$, but in the entirely different and restricted *thermodynamic* sense that it has been irreversibly transformed and cannot in consequence further serve as a source of available energy, either for growth or for maintenance.

But it is also known (*ii*) that growth is accompanied by the liberation of heat.

* See footnote p. 27.

The significant features of this phenomenon, gained from common as well as from experimental observation (see Needham, 1931), may be summed up in the statement that, aside from certain exceptions later to be noted, the production of heat per unit mass by a "growing organism" exceeds that of a similar organism which is familiarly said "not to be growing." More specifically, we have

$$(6) \qquad \left\{\begin{array}{c}\text{Heat output per unit mass}\\ \text{by a growing organism in}\\ \text{any one of the states:}\\ [q>0,\ \dot{q}>0,\ \ddot{q}\gtreqless 0]\end{array}\right\} > \left\{\begin{array}{c}\text{Heat output per unit mass by}\\ \text{a "nongrowing" organism, i.e.}\\ \text{by one in the stationary state:}\\ [q>0,\ \dot{q}=0,\ \ddot{q}=0]\end{array}\right\}.$$

If, then, growth be dynamical, as we hope to show, it is on the basis of item (*ii*), clearly, that we may identify growth as a nonconservative dynamical mode of motion, but we are not as yet in position to say whether heat so liberated is *dissipated* in the dynamic sense or whether it is due to other nonconservative actions arising out of the motion of growth. Nevertheless, we are now able to infer from (*i*) and (*ii*) that heat production by systems undergoing growth (excluding, of course, such heat as might arise from spoilage or decomposition from extraneous causes) consists of two parts and is therefore in general accountable to one or both of two chief forms of action: (*a*) *maintenance* of the organism and (*b*) *growth* of the organism, the former being, in the classical sense, certainly adynamic, the latter, for the present, presumably dynamic.

Maintenance is concerned, in virtue of the property of life, solely with the preservation of body substance, form, function, and organization; and it is obviously a necessary condition to the persistence of a cell. Somewhat paradoxically, it is thus in the nature of growth, which is self-multiplication, to destroy by its motion the very identity of that, the cell, which maintenance is concerned in preserving; and from this it is clear that the concept of maintenance must immediately be extended beyond that of preserving cellular identity to include maintenance of body substance, form, function, and the composite organization of living things in a state of simple existence.

In order properly to understand the significance of the preceding facts designated as (*i*) and (*ii*) above, as well as the inferences just drawn from them, it will be best to review certain important physiological situations which have not required explicit mention until now.

Let us compare, for instance, the adult or fully matured member of a species with an individual infant of the same species. The former is in a state of simple existence, that is, of rest with respect to growth; the latter, clearly, is in a state of motion. Given identical conditions of physical repose, the former requires a certain minimum quantity of energy for continued vegetative existence (Lusk, 1928). If this be supplied, body mass remains constant, provided, as is usual, an equivalent amount of heat is simultaneously liberated by the organism. This, then, we shall call the *heat of maintenance*. It will be more precisely defined below. Now, an infant under similar basal conditions will likewise produce heat, but this will always be greater per unit mass of tissue than that of the adult, whether the balance between intake of energy and output of heat is adjusted at

levels such that (*a*) no gain or (*b*) normal gain is permitted; in the latter case (*b*), the infant will not only require still more energy per unit mass than in (*a*), but it will also liberate a correspondingly greater quantity of heat, and again, in either case, more than the adult (Czerny, 1923). Further, if M' be the minimum quantity of energy per unit mass required by the adult in unit time to provide for pure sustenance alone, the administration of the same quantity per unit mass and time to an infant will promptly be followed by a loss of body substance. Incidentally, it is thus clear that comparisons of energy requirements, or of heat liberated, cannot be correctly made on the basis of "preservation of weight" alone. For all such purposes we need explicitly to specify the state of growth in which weight is held constant. The standard of reference is obviously the state of rest $[q>0, \dot{q}=0, \ddot{q}=0]$, when naturally and not artificially* attained. Hence, we shall define the *heat of maintenance* as the heat liberated by an organism in the naturally attained state of growth $[q>0, \dot{q}=0, \ddot{q}=0]$, when the organism, in addition, is kept under circumstances of complete physiological repose, that is, under what are commonly called basal conditions. This will be equal to the *energy of maintenance* which is meanwhile required and being used solely to nourish the organism under the same conditions.

Since the tissues or body of an infant are just as much in need of nourishment, for the sake of simple existence alone, as those of the adult, it is clear that, if growth could be halted other than by limiting the supply of energy and without undesirable side effects, infant and adult would require, per unit mass and time, an identical quantity of energy and would liberate an identical quantity of heat. Thus, the *heat of maintenance per unit mass per unit time* is to be taken constant for the species and we shall denote it by A'_j, with the understanding that $A'_j>0$ and is constant for the species j. Similarly, let M'_j be the energy per unit mass and time supplied and utilized for maintenance by a member of species j, whence, for the conditions defined,† we have,

$$M'_j = A'_j = \text{constant} > 0. \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{7}$$

This balance of maintenance energy supply and heat output will hold for every healthy organism, irrespective of its state of growth; but, as we have seen, if the organism be in the motion of growth, basal heat output will be greater than that accounted for simply by maintenance. In fact, the excess will be due to growth, and can therefore be called the *heat of growth*, which, for the same units as above, we denote H_g. Hence at any stage of growth, if U be composite heat output per unit mass and time, for any species j, we may write,

$$U = H_g + A', \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{8}$$

since the subscript j will no longer be required.

The calorimeter, however, cannot serve to identify H_g or A', separately, and hence cannot distinguish between them, for measurements of heat are obviously

* Most usually accomplished by restricting fuel, a condition contrary to the original stipulation of unaltered food supply.

† The case $(M'-A')\gtrless 0$ will be discussed later.

those of the sum U. Moreover, since $A'>0$, it might be thought that we will always have $U>0$, H_g being clearly understood to vanish in the stationary state $[q>0, \dot{q}=0, \ddot{q}=0]$, that is, with the vanishing of $\dot{q}$ or $\ddot{q}$ (whether this will depend only upon the vanishing of $\dot{q}$ or of $\ddot{q}$, or again of both, cannot of course, be determined from the evidence thus far brought forward). But $U \gtreqless 0$ can and does occur, irrespective of the values of $\dot{q}$ and $\ddot{q}$, whence, since $A'>0$, we must necessarily be prepared to expect values of $H_g \gtreqless -A'$. Usually $U>0$, and $H_g>0$, when $\dot{q}>0$.

The Dual Character of the Heat of Growth, H_g; Heat of Dissipation, H_d; Heat of Synthesis, H_c.—Thus, the fact that $H_g>0$ usually, taken in conjunction with the further fact that $H_g \leqq 0$ under certain important conditions, suggests that the quantity H_g is composed of at least two parts. Recalling, now, that H_g is associated distinctly with the *motion* of growth and hence more particularly with $\dot{q}$ or with $\ddot{q}$ than with q itself, we need first to distinguish between these possibilities. On general dynamical theory we should not expect H_g to be directly concerned with the acceleration $\ddot{q}$ at all, since quantities of this kind are characteristically involved in inertial reactions (next to be discussed), and since the latter, in turn, are of the conservative rather than of the nonconservative class to which H_g clearly belongs. We are therefore led to infer that the two parts already suspected to exist in H_g can involve $\dot{q}$ only, and hence must be two different functions of $\dot{q}$ itself. Other facts point to the same conclusion.

First, let us recall that growth is an irreversible event accomplished by irreversible processes in the sense that daughter cells once fashioned surely never reunite to form their own antecedent mother cells. The underlying motion which effects growth, and which is thereby responsible for the production of daughter cells, must likewise be irreversible in the same sense. Then, again, we do not see growth become initiated by random chance, nor of its own accord; but, we do see it dying away, as though of its own accord, toward some ultimate equilibrium level $q_f \gtreqless q_0$, as mentioned in connection with Figure 1. The approach to the stationary state $[q>0, \dot{q}=0, \ddot{q}=0]$ is, moreover, always a gradual one, whether from above or from below, and, what is of distinct importance, heat continues to be liberated throughout either of these episodes and must therefore be independent of the sign of $\dot{q}$. We cannot possibly avoid the extremely important conclusions (*i*) that some property of the system is very definitely concerned with the inevitable retardation in q; (*ii*) that its action is not affected by the sign of $\dot{q}$; and (*iii*), since heat and retardation are both manifested simultaneously and continuously, no matter what the direction of approach to q_f may be, that these separate effects are due to the common action of *motional dissipation*, which must involve even, and clearly not odd, powers of $\dot{q}$ at all.

Investigation of the latter point has indeed shown that, in some of the simpler systems (where more complicated situations are either not operative or are negligible), the rate of heat production per unit mass is actually linear in $\dot{q}^2$ (Wetzel, 1932–33 *f*). This portion of H_g we shall call the *heat of dissipation*, H_d*;

* Strictly, heat of dissipation per unit mass and time; the heat of dissipation itself would be given by $\int(H_d x)dt$.

further, if H_c be the remaining portion of heat in H_g, we obviously have $H_g = H_d + H_c$, and hence, for composite heat output per unit mass and time,

$$U = H_d + H_c + A' \qquad [\text{cal} \cdot \text{gm}^{-1} \cdot T^{-1}] \tag{9}$$

for all states of growth.*

Thus, since H_d and A' are essentially positive, it is clear that H_c must be the portion responsible for the aberrant values, $H_g \gtrless 0$, that are occasionally encountered. In such cases H_c oscillates between negative and positive values, in particular between $-(H_d + A') < H_c > 0$. Now, H_c is intrinsically associated with growth in motion $[\dot{q} \gtrless 0, \ddot{q} \gtrless 0]$, and, since it cannot, as a nonconservative action, be held assignable to $\ddot{q}$, nor, from what has just been said, depend on any even power of $\dot{q}$, it must, in first approximation, be linear in $\dot{q}$ itself. This, we shall again be able to verify experimentally. For more explicit reasons later to be given, H_c will be called the *heat of synthesis per unit mass per unit time.*

Since the evidence now presented clearly justifies the assumptions, $H_d = f_1(\dot{q}^2)$, and $H_c = f_2(\dot{q})$, equation (9), without any knowledge of Φ in (5), could be put directly to experimental test, with the hope of checking the forms of f_1 and f_2. A purely empirical attempt of this kind would have but limited usefulness. We propose here, instead, to continue the treatment along general dynamical lines, in particular, to regard H_d as an effect which may be represented by a modification of Lord Rayleigh's dissipation function. This step is deferred, for the present, because we are primarily interested just now in characterizing not a part, but rather the whole of those actions upon which the motion of growth depends.

In summarizing the foregoing results, we may place systems supporting growth provisionally in the general class of dissipative dynamical systems occurring in nature. This has depended, explicitly, as we have just seen, upon the recognition and identification of H_d, and not simply upon the fact that growing organisms liberate heat. We have meanwhile learned to distinguish critically between the *heat of maintenance* and the *heat of growth*; and we have found that the latter consists, in general, of at least two individual portions, both motional since they involve $\dot{q}$ somehow, and both nonconservative in the dynamical sense, but the one (H_d) *dissipative*, and the other (H_c) not of this type.

The Inertial Property of Growth in Motion and at Rest

Inertia of Motion.—We pass next to a consideration of another set of facts which, taken together, point directly to the existence of a quite different yet equally important property of systems that support and exhibit growth. We

* The term metabolism, widely used in clinical work in connection with estimates of heat production and energy exchange, both in health and in disease, is not always clearly defined. From what has been said it will be evident that it refers to the maintenance output of heat in organisms that have reached the stationary state, but that it refers in growing organisms to the sum of maintenance heat *plus* heat due to growth. It is advisable, moreover, to avoid possible confusion in units. We shall, therefore, understand the term metabolism to mean the energy transformed into and measured, either directly or indirectly, as heat, when expressed, irrespective of the state of growth, in terms of calories per unit of mass and time, provided that these estimates are made, wherever possible, under the usual standard conditions of observation. Estimates of metabolism will therefore be estimates of U as given by equation (9) and later by (38).

refer specifically to the property of *growth inertia* and in association with this, to the *kinetic energy of growth in motion*. While comparatively little or no attention has heretofore been given to this aspect of the subject, the main facts are easily gathered and can be discussed most briefly. We shall bring forward at this stage only those data of experience (see Fauré-Fremiet, 1925) that are necessary and sufficient to establish the existence of growth inertia; the formulation of the kinetic energy function, like that of the dissipative function already mentioned, is deferred until later.

The biological permanency which every species displays in its past history is merely an outward and highly modified expression of the inertia of growth; to attempt an analysis of these cases we should be obliged to discuss actions and reactions among multicellular forms in systems whose complexity is obviously beyond the range of our present studies.

But in the single organism of multicellular structure, or in any unicellular population, we see even more clearly that growth, once initiated, *tends* to remain in motion. It is well to consider a few relevant details on this point.

Examples from Ordinary Subcultures.—Here, again, as is so frequently the case, we turn with profit to examine the phenomena exhibited in cultures of unicellular organisms, for the important facts are not so readily obscured in such examples by otherwise less significant events. Let a series of subcultures, c_a, c_b, c_c, $\cdots$, be made from a suitable mother culture as it passes through the corresponding "phases" (a), (b), (c), $\cdots$, in Figure 1, the nutrient media and all other physical conditions being kept the same during the subsequent growth of the subcultures. Abundant evidence* has shown that growth in each subculture will continue in the form and at the rate typified by the respective phase in the mother culture from which it had been removed. Thus, subculture c_a will become initiated in, and will continue through a stage having the characteristics of (a); later, of course, it will pass through stages similar to (b), (c), (d); subculture c_b will not display the lag represented by (a) but it will exhibit logarithmic growth from the start, the rate of growth, for practical purposes, being identical with that of the mother culture. This will continue until culture c_b is acted upon to alter its course and to enter the later phases of retardation (c) and rest (d). Precisely the same is true if subcultures are made along (e_1) and (e_2); for in every instance of this kind, growth in a subculture continues in the manner and at the rate of its mother culture. The persistence of velocity, on subculture, is thus established for those cases in which the subinoculation is made into a nutrient medium like that originally serving as the source of energy in the mother culture.

Examples in Neutral Media.—An important corroboration of the property of growth inertia is even more strikingly displayed when the subculture is placed into a medium, such as Tyrode's solution, that possesses no essential source of energy and cannot, accordingly, be said to supply energy for growth. Yet, just

* See, for example, Barber (1908), Carrel (1923), Carrel and Burrows (1910), Carrel and Ebeling (1921), Chesney (1916), Ebeling (1922), Harrison (1907, 1910), Ledingham and Penfold (1914), McKendrick and Pai (1911), Richards (1928), and Woodruff (1928–29).

as before, growth persists, for a short, but nevertheless easily measurable period of time, at a velocity equal or almost equal to that in the mother culture. This phenomenon has been called "residual growth" (Carrel, 1923), but it belongs more properly to the class of true inertial effects. It is not dependent upon the size of the subculture, except when the distribution of velocities of growth which the individual members of a subculture possess is not uniform, a fact that obviously explains, in part, the widely known difficulty in successfully culturing single organisms.

The inertial property of growth in motion cannot, therefore, depend directly on the position $(q_r)_m$ which the mother system, designated by the symbol $(\ )_m$, has reached at $(t_r)_m$, the moment at which the seed is removed; it must, instead, depend rather on the velocity $(\dot{q}_r)_m$ and acceleration $(\ddot{q}_r)_m$ of growth in the mother culture at $(q_r, t_r)_m$, and in support of this it is necessary merely to note that the initial and immediately succeeding velocities $(\dot{q}_0, \cdots)_{sc}$ and accelerations $(\ddot{q}_0, \cdots)_{sc}$ in the subcultures $(\ )_{sc}$ are positive or negative in strict accordance with the signs of $(\dot{q}_r)_m$ and $(\ddot{q}_r)_m$ in the original mother culture. Again, of course, as mentioned before, $(\dot{q}_0)_{sc} \cong (\dot{q}_r)_m$; and $(\ddot{q}_0)_{sc} \cong (\ddot{q}_r)_m$.

Inertia of Rest.—We shall accept this evidence, then, as a sufficiently convincing demonstration that growth, once initiated, tends to remain in motion; the corollary that it likewise tends to remain at rest, if already in a stationary state, is fully established by the fact that subcultures made during the lag and stationary phases (*a* and *b* in Fig. 1) are conspicuous examples of failure to "grow out." The most successful subcultures are made, as all who work with them know, when the mother culture is in the logarithmic phase of growth (*b*, Fig. 1), that is, analytically, when $\dot{q}$ is approximately maximum for the actual conditions of observation.

The information just now brought forward may therefore be summed up in the statement: *Cellular reduplication, once initiated, will continue uniformly in its state of motion until acted upon to change that state.* Even though this particular formal expression of the facts is not wholly subject to experimental proof (for there are no vessels in which the overwhelming yield could be stored, nor is there a source of sufficient energy to supply the resulting demand), we must recognize that no known fact is contradictory to it. We are therefore compelled to accept the property of growth inertia, that is, the property by which the velocity of growth tends to persist under constant conditions, as a distinct attribute of systems that support growth; and we may conclude that, if growth be dynamical, it possesses the dynamical property of growth inertia. Its connections with the acceleration, $\ddot{q}$, will be developed later in setting up a corresponding kinetic energy function.

The Positional Properties of Growth

We have now to consider the positional as opposed to the motional properties of systems supporting growth, and, in the course of this objective, to present the information which will later justify our setting up a potential energy function. We have therefore to deal with agencies that depend on the position of the sys-

tem as given by q itself, rather than, as before, with $\dot{q}$ and $\ddot{q}$, which are directly concerned with the motion of growth. The evidence on this point is likewise readily collected and it does not need to be abundant; for, we have only to inquire whether the rate of growth, other things being equal, *is* or *is not* influenced by the presence of a greater or lesser population size, and hence by the corresponding effect of the position q which the system has attained at any time t.

The evidence is conclusive.* We shall present it from three different but closely related points of view. Collectively, the results will show that the rate of growth depends, among other things, on the displacement of the system from some position of stationary equilibrium q_f.

Position in a Neighborhood of Equilibrium.—To begin with, it has already been pointed out in connection with Figure 1 that the equilibrium position q_f may be above, at, or below the initial position q_0, that is, we shall in general have values such that $q_f \gtreqless q_0$. Consider, now, the simplest experimental case consisting of a series of identical systems ($s=0, 1, 2, \cdots, f$) in which the equilibrium position is fixed at a level such that $q_f > q_0$ and q_0 not negligibly small with respect to q_f. Suitably arranged cultures of unicellular organisms are again the example of choice, although the phenomena now to be described are just as forcibly displayed in other more complicated cases of growth (Ellis, 1909).

Let the initial quantity of growth $(q_0)_s$ be varied in each of the s individual systems and let the corresponding initial values of velocity be $(\dot{q}_0)_s$. For these conditions, it is known, from good experimental evidence of the kind just mentioned, that $(\dot{q}_0)_s \to 0$ as $(q_0)_s \to q_f$. At the limit when $(q_0)_{s=f} = (q_0)_f = q_f$ we ought, therefore, to have $(\dot{q}_0)_{s=f} = (\dot{q}_0)_f = 0$. While this critical case has never itself been made the subject of experimental test in examples such as we are considering, there can be little doubt that the point could be substantiated, because it is known, in addition to what has been given for the case $(q_0)_s < q_f$, that a similar sequence of events, with the signs of the velocity reversed, will take place when $(q_0)_s > q_f$, that is, $(-\dot{q}_0)_s \to 0$ from *below* as $(q_0)_s \to q_f$ from *above*. (See Graham-Smith, 1920–21, and G. S. Wilson, 1922.)

In order to gain greater insight into the real significance of these results let us next give them in the obviously equivalent form: $(\dot{q}_0)_s \to 0$ as $q_f \to (q_0)_s$, wherein we simply regard the equilibrium level q_f as arbitrarily variable and the initial value of the seedings $(q_0)_s$, as fixed. Thus, other things being again equal, the rate of growth depends upon the displacement of q in the system from its ultimate position of equilibrium, and it is now clear that this result is related directly to the effect of the position characterized and represented by q_f itself.

The facts just described are considered, as indicated, with respect to the influence of positional changes on the rate of growth only in the neighborhood of the initial values, $(\dot{q}_0)_s$, and hence only with respect to the initial states, $[q_0, \dot{q}_0]_s$. Similar effects, however, may also be discerned in studying the succeeding states of growth in each of the individual s cultures, for the rate of growth diminishes as the position of equilibrium q_f is approached. Thus we have, quite generally,

* See Brown (1905) Ellis (1909), Montank (1928), and Richards (1928).

and irrespective of whether we deal with initial or with subsequent states of growth, $(\dot{q})_s \to 0$ as $(q)_s \to q_f$.

We may conclude that the rate of growth is sensitive to the position of the system relative to that of equilibrium, and hence to the effects of position *per se* that are exerted by the quantity of growth which the system has accumulated. But to put the matter beyond any possible doubt, let us now consider the following corroborative results.

Position Remote from Equilibrium.—Thus far, we have been describing specifically the dynamical effect which the quantity $(q_f - q_0)$ can be made to exert upon the initial and subsequent rates of growth, and we have seen first that $(\dot{q}_0)_s \to 0$ as $(q_f - q_0) \to 0$ irrespective of whether we take $q_f \to q_0$ or $q_0 \to q_f$, provided only that q_0 is not negligibly small with respect to q_f. We have also seen, for values succeeding the start, that $(\dot{q} \cdots)_s \to 0$ as $(q \cdots)_s \to q_f$. Now, however, let q_f increase indefinitely so that q_0 does become negligible as compared with q_f, in other words, let arrangements be made whereby the ultimate level of equilibrium represented by q_f is raised far above that which would be reached when other conditions remain the same, for example, as in the interesting work of Richards (1928) on potentially unlimited growth in yeast. In such an experiment we find, as we should, if positional effects actually exist, that the initial *as well as* subsequent values of the rate of growth in the s subcultures are now identical, that is, $(\dot{q}_0, \cdots)_1 = (\dot{q}_0, \cdots)_2 = (\dot{q}_0, \cdots)_f = (\dot{q}_0, \cdots)_s$. But it is also found that $(\dot{q}_0, \cdots)_s =$ constant as long as the original circumstances of growth remain unchanged. Here, then, the cell population is evidently released from the positional effect of equilibrium q_f: the rate of growth in all of the s systems is the same; it remains constant, and equal to the rate which each of the systems could originally support. We therefore have, in the present notation, $(\dot{q} \cdots)_s \to (\dot{q}_0)_s$ as $q_f \to \infty$. The s systems, accordingly, are no longer subject (theoretically speaking) to the effect of position, specifically that of equilibrium, which had previously led to the result that $\dot{q} \to 0$ as $q \to q_f$. These properties likewise justify the conclusion that we must expect q_f to consist, as we shall later see, of two distinct parts.

In actual practice, however, growth will always take place in some neighborhood of equilibrium, and it is therefore clear that the accumulation, or simply the presence of a quantity of growth q within such a neighborhood, will have a distinctive and recognizable effect on the accompanying as well as upon the ensuing rate of growth $\dot{q}$. From the dynamical point of view this result is sufficient to justify setting up a corresponding potential energy function of growth.

Finally, to summarize the evidence thus far reviewed in respect of various phenomena which systems sustaining growth are now seen to display, it may be said that systems of this kind are characterized as nonconservative fields of action wherein three chief types of energy transformation are readily distinguished. These are: (*i*) the kinetic energy of growth in motion, the existence of which we deduce as a corollary of the conspicuous property of growth inertia; (*ii*) the transformation of energy into heat; and (*iii*) the energy associated with the position q, or the so-called energy of configuration, whose effect upon the

rate of growth we have examined in regions near to, as well as remote from, stationary equilibrium. This, briefly, is the evidence which suggests that growth, already viewed on purely kinematical grounds as a mode of generalized motion, may properly be treated by the methods of classical dynamics.

Lagrange's Method as Applied to the Problem of Growth

In now coming to the formal development of the present theory, it would appear promising, on the basis of the foregoing results, to make use of the Lagrangian equations for the case of nonconservative generalized motion.* If we limit ourselves at the outset to the case of motion with one degree of freedom as exemplified by the curve of Figure 1, we could begin with,

$$\frac{d}{dt}\left(\frac{\partial T}{\partial \dot{\psi}}\right) - \frac{\partial T}{\partial \psi} + \frac{\partial F}{\partial \dot{\psi}} + \frac{\partial V}{\partial \psi} = P, \qquad [ML^2T^{-2}][\psi^{-1}] \tag{10}$$

in which, with the usual notation, T is the kinetic energy, F the dissipation function introduced by Rayleigh (1894), V the potential energy of the system, and P the generalized component of force, or, as it is also called, the external force applied to the system. It is understood, for the present, that T and F are functions of the velocity of the generalized coordinate, namely, of $\dot{\psi}$, whose coefficients may involve ψ, whereas V is a function of the coordinate ψ only. It is also understood that P has the dimensions Energy/ψ, so that the product $P\delta\psi$ denotes the work done by the external forces in an arbitrary displacement $\delta\psi$ of the generalized coordinate ψ.

But the admissibility of equation (10) to the present problem depends entirely upon the possibility of obtaining satisfactory solutions to several very important questions. It would depend in the first place either upon the discovery of explicit connections between the three types of energy transformation, whose existence has turned our attention to (10), and the three mechanical functions T, F, and V contained in that equation, or, failing this, upon the possibility of finding other functions equally suitable for the role which T, F, and V take in (10). We must therefore be prepared to expect not only that (10), but even more fundamentally than this, that the concept of energy can serve the present problem only in so far as it will prove possible to develop a theory of growth by the methods of mechanics. But, in addition to the matters just mentioned, we shall also have to discuss the possibility of choosing some accessible part of the systems under discussion which might be taken to represent the generalized coordinate ψ. Not until then can we begin to study other relationships contained in equation (10).

Mechanical Kinetic Energy, T; Kinetic Energy of Changing Size, T_s, and Kinetic Energy of Growth, T_m.—It is familiar from mechanics that the kinetic energy T appearing in (10) is defined for a system of particles as,

* See Ames and Murnaghan (1929), Kelvin and Tait (1912), Lindsay and Margenau (1936), Webster (1904), and Whittaker (1927).

$$T = \frac{1}{2}\sum_{i=1}^{n} m_i v_i^2,$$

where m_i is the mass and v_i is the space velocity of the ith particle. In such a system each mass, m_i, is assumed to be *constant* during its space displacement. But it is precisely in the nature of growth that the mass of an organism does not remain constant, at least not during the usual epochs with which the term growth is commonly associated. Now, while the reason just given is by no means the only one to show that the three varieties of kinetic energy we have henceforth to keep in mind, namely, mechanical kinetic energy T, kinetic energy of changing size T_s, and growth kinetic energy T_m, are not identical, it will nevertheless help to indicate their similarities.

Mechanical kinetic energy is associated with mechanical inertia, that is, with the property by which a particle could ideally maintain a constant vector velocity with reference to an appropriate frame known as an inertial frame. A change in velocity only will change the kinetic energy of such a particle.

In the case of growth, there is an analogous situation whereby cells once initiated into a state of multiplication *tend*, as we have already remarked, to continue *growing* at some constant rate, say $\dot{q}_1$. Now, it is most important to note, however, that, although growth may be proceeding at the constant rate $\dot{q}_1$, the cells themselves are accumulating at the corresponding variable rate, $\dot{z} = z\dot{q}_1$ in view of (4). Thus, even though we might be led to take the kinetic energy of changing size, or cell number as in this case, T_s, to be a function of the rate of growth $\dot{q}$, it is clear that T_s must also depend upon cell number z_n, or in general simply upon size z, as well as upon the time.

Consider this case more fully where, as noted, a suitable culture of unicellular organisms is maintained throughout an interval of time $t_0 \rightarrow t$ in the "logarithmic phase" (c in Figure 1) at the constant rate of growth $\dot{q}_1$. If, now, the concept of energy can be applied at all, we shall have to regard the kinetic energy of changing size, T_s, associated with rate $\dot{q}_1$ as different from that associated with all other rates $\dot{q}_r \neq \dot{q}_1$ which might conceivably have been induced during the same interval; further, since the kinetic energy of changing size is implicitly proportional to population size (or mass), we see that T_s must increase as the culture contains more and more daughter cells, and hence, as time advances. But this increase in T_s is occurring under the very conditions, and throughout the same interval, in which the rate of growth, $\dot{q}_1$, remains constant. Thus, while both T and T_s have the dimensions of energy, and depend on their respective velocities, T remains constant with constant velocity of space displacement, whereas T_s increases even though $\dot{q}$ remains the same. It is therefore evident that, although T and T_s are dimensionally alike (both being energy), they do not possess identical properties with reference to their respective systems.

But it is easy to see that the essential dynamical property, by which T in the mechanical case remains constant for constant values of space velocity, may likewise be secured for the case of growth if we choose, wherever mass is the measure of size, a new quantity, $T_s/\Sigma m_i = T_m$, most naturally designated as the

kinetic energy of growth, with the dimensions of *energy per unit mass*, in place of T_s, provided that the generalized coordinate velocity $\dot{\psi}$ be taken as $\dot{q}$; for T_m in the case just cited will then remain constant, for constant values of $\dot{q}$, throughout the interval $t_0 \rightarrow t$ and will be a function of $\dot{q}$ alone. We have therefore to see whether the choice of $\dot{q}$ as a generalized velocity will satisfy other conditions of the problem.

The Generalized Coordinate, q.—The most accessible *parts* of a system undergoing growth are the cells, tissues and bodies of organisms, their sources of fuel supply, and the environment in which they exist. But the most accessible *features* of such systems are the changes in size, more particularly, changes in number, mass, length or in some function of length, that accompany the comparatively concealed mechanisms of cell division and differentiation. All of these changes, however, are not independent, for changes in mass are correlated under conditions of healthy and normal growth with changes in length, cell number or volume, as well as with quite characteristic, but again, not independent changes in shape. In addition, *change in size*, as we have seen, is not of itself the most pertinent measurable feature of biological growth. The latter, in fact, is rather the quantity of growth q as defined by equation (4) in terms of z, the size of an organism or of a cell population. But the quantity q is actually an accessible feature of these systems because it depends explicitly upon z, and the choice of q to represent ψ will obviously satisfy the kinematical conditions represented by the curve in Figure 1.

Furthermore, in the case of one degree of freedom, that is, again, in the case of a single multicellular organism, or for a unicellular population of similar cells, q will be the only coordinate required, for q itself is sufficient to define the position of a system in the inertial frame of growth, which is taken to be a frame, like that illustrated by Figure 1, with respect to which $\dot{q}$ is measured, the origin of q coinciding with a possible position of equilibrium. Additional coordinates, say, $\psi_2, \psi_3, \cdots, \psi_n$ would therefore be required only when two or more organisms, or two different varieties of unicellular populations, are to be treated as independent competitors for energy from a common source.

Finally, if q represents ψ, $\dot{q}$ will become a generalized velocity, and the desirability of this has already been emphasized in connection with the distinction as well as with the similarities between T, T_s and T_m.

We have, then, on introducing T_m, q and $\dot{q}$ into (10),

$$\frac{d}{dt}\left(\frac{\partial T_m}{\partial \dot{q}}\right) - \frac{\partial T_m}{\partial q} + \frac{\partial F_m}{\partial \dot{q}} + \frac{\partial V_m}{\partial q} = P_m, \quad [\text{cal}\cdot\text{gm}^{-1}][\text{q}^{-1}] \tag{11}$$

where F_m, V_m, and P_m bear the same relationship to F, V, and P that T_m bears to T, so that F_m is now to be considered power per unit mass instead of power simply, and V_m potential energy per unit mass in place of potential energy. For reasons presently to be explained, it will be convenient to call P_m the *net external*, instead of simply the *external* generalized impressed force per unit mass acting along the coordinate q. Meanwhile it is sufficient to understand that P_m

represents the applied force that balances the three reactions of the system on the left of (11).

The associated equation of activity,

$$\left\{\frac{d}{dt}\left(\frac{\partial T_m}{\partial \dot{q}}\right)\right\}\dot{q} - \frac{\partial (T_m - V_m)}{\partial q}\dot{q} + \frac{\partial F_m}{\partial \dot{q}}\dot{q} = P_m\dot{q}, \quad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{12}$$

would therefore be expressed in terms of energy per unit mass and time.

But even apart from the foregoing questions, or from the nature of the relations between T_m, F_m, V_m, and q or $\dot{q}$ which still confront us, it can be seen that equations (11) and (12) will not be suitable to the present problem since the heat output of growing organisms which consists of the three different portions in U of equation (9) cannot be accounted for by F_m alone.

Modification of the Lagrangian Equation to Include Composite Heat Output.— Equation (10) as originally contemplated for nonconservative mechanical motion provides only for the single item of heat represented by F. In the case of growth, however, there are, besides F_m in (12), two additional reactions on the part of such systems which culminate in heat, namely, H_c, the heat of synthesis, and A', the heat of maintenance. These combine with the heat of dissipation, H_d (presumptively related to F_m), to form the composite heat output U as given by equation (9). This situation is peculiar to the motion of growth, as compared with other forms of generalized motion in systems whose parts do not require energy for, nor liberate heat as a result of, construction (synthesis) or nourishment. The problem may be treated much as in the inanimate cases in mechanics when, for example, gyroscopic or other effects are given explicit attention. For equations (9) and (12) are dimensionally alike and we may replace the single item of heat represented by $[(\partial F_m/\partial \dot{q})\dot{q}]$ with U, provided that the additional heat reactions H_c and A', just mentioned, are balanced by the introduction of suitable components on the right of (12). Thus, the complete equation of activity for growth and maintenance combined finally becomes

$$\left\{\frac{d}{dt}\left(\frac{\partial T_m}{\partial \dot{q}}\right)\right\}\dot{q} - \frac{\partial (T_m - V_m)}{\partial q}\dot{q} + U = P_g\dot{q} + M', \quad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{13}$$

where M' is the power per unit mass delivered, whether $\dot{q} \neq 0$ or not, for the purposes of maintenance represented by the nonmotional reaction of heat A' contained in U, and where P_g is now called the generalized *external* impressed force per unit mass in contrast to the *net external* force P_m in equation (11). The P's will then be connected by the relation,

$$P_g - P_c = P_m, \tag{14}$$

where P_c is the force component corresponding to the motional reaction H_c likewise contained in U.

Equation (13) now represents the Lagrangian equation of activity as modified for the case of growth, and it includes explicitly not only the three main effects ascribable to growth itself but also the equally important biological item of

maintenance as well. The several items of work thus far identified and explicitly given on the left of (13) in terms of power per unit mass, now comprise all of the portions for which definite experimental evidence can be adduced. In addition to these there may, of course, actually be other portions of work such as that which is accompanied by various types of radiation other than that of heat, but there are no data at present available by which this possibility can be tested (see Snyder, 1931; Needham, 1931). Yet, granting that radiation other than heat can be shown to be appreciable, it seems unlikely, even now, that this would require an additional term on the left of (13), for we should first expect that energy so radiated could be accounted for in T_m, in V_m, or even through the combined effect of these two fundamental attributes of systems supporting growth.

To sum up, it may therefore be said that the energy which a growing organism requires is converted into work associated, first, with the kinetic energy of growth, T_m, and hence, in general, not only with the momentum of growth $(\partial T_m/\partial \dot{q})$ but also with the nonmomental kinetic reaction $(\partial T_m/\partial q)$; second, with the energy of position, V_m, and, finally, with the remaining portion U that is transformed into heat. In these general respects the left hand side of (13) is equivalent to the corresponding equation of activity in physical dynamics, the distinction between the two equations being expressed mainly by the fact that, although U itself refers to heat, just as the dissipation function F of Rayleigh also does, U is not identical with F in the present biological problem of growth.

Before equation (13), however, can be applied to actual cases of growth it will first be necessary to evaluate the three functions T_m, V_m, and U in terms of q or $\dot{q}$ as the case may be. We shall then be able to deal with P_g separately.

The Kinetic Energy of Growth, T_m, in Terms of $\dot{q}$.—From what has already been said of the nature of T_m in connection with the property of inertia, and from the selection of q as the Lagrangian coordinate of the system, we assume (as in mechanics), for any given position relative to the inertial frame of growth, that

$$T_m = \tfrac{1}{2}\lambda(q)\dot{q}^2 \qquad [\text{cal}\cdot\text{gm}^{-1}] \tag{15}$$

represents the kinetic energy of growth*, where $\lambda(q)$ is defined as the *inertia coefficient of growth*. As indicated in equation (15) this coefficient will depend, in general, upon the positional coordinate q. But for the most important cases that arise in practice, which always consist of motion in a neighborhood of equilibrium, we may employ only the constant term λ_0, that is, the value of $\lambda(q)$ at equilibrium, since the variable terms in $\lambda(q)$ may then be considered negligible in comparison with λ_0.† In the latter case, T_m will not depend explicitly on the coordinate q, so that the nonmomental part of the kinetic energy in (13), $(\partial T_m/\partial q)$, will vanish and q will therefore become a cyclic coordinate.

The Potential Energy of Growth, V_m.—It has already been shown‡ that posi-

* Dimensionally, energy per unit mass. See p. 27 ff.

† The subscript in λ_0 may henceforth be dropped.

‡ See p. 24 ff.

tional effects are exerted through the agency of the parameter q and we have therefore concluded that a portion at least of the energy of a system may be derived from a potential energy function. The associated generalized positional forces will help to determine the corresponding time-rates of change of the coordinates. If, then, as here, the configuration of the system be defined by the coordinate q, the potential energy will depend on q alone and not upon its derivatives. Thus, employing Taylor's theorem, we get the expansion,

$$V_m = V_0 + \left(\frac{\partial V_m}{\partial q}\right)_0 q + \frac{1}{2}\left(\frac{\partial^2 V_m}{\partial q^2}\right)_0 q^2 + \cdots, \tag{16}$$

wherein the subscript $(\ )_0$ refers to the values of the partial derivatives when $q=0$. If $\dot{q}$ and $\ddot{q}$ are also zero, the position $q=0$ will be an equilibrium one, and V_m, in consequence, will be either maximum or minimum, so that $(\partial V_m/\partial q)_0 = 0$. Omitting further consideration of V_0, since the potential energy of growth will always involve some arbitrary constant, and since the latter in turn has no effect of its own upon the resulting motion, we may, clearly, put

$$V_m = \frac{q^2}{2\kappa} \qquad [\text{cal}\cdot\text{gm}^{-1}] \tag{17}$$

as an approximation to equation (16) above, where κ is defined as the *permittance of growth*, and where $1/\kappa$ has the value $(\partial^2 V_m/\partial q^2)_0$. Finally, if the equilibrium be stable, V_m is minimum, and since V_m is essentially positive, we must have κ positive.

The Function U.—It has previously been learned in connection with the discussion of U as represented in equation (9) that heat liberated by a growing organism must be considered to be of two main kinds, (*i*) a part arising out of the motion of growth *per se*, H_g, consisting of the two subportions H_d and H_c, and (*ii*) a part, A', ascribable to the maintenance of life, which is wholly independent of growth. We shall now consider the functional relationships between both of the former and the rate of growth $\dot{q}$.

The Heat of Dissipation, H_d, in Terms of $\dot{q}$.—If the nonconservative generalized component of force per unit mass, P_d, associated with the reaction F_m in (11) and thus contained in P_m, be proportional to the first power of the time-rate of change of the coordinate q, that is to $\dot{q}$, we have,

$$P_d = \rho\dot{q}, \qquad [\text{cal}\cdot\text{gm}^{-1}][\text{q}^{-1}] \tag{18}$$

where ρ is a constant of proportionality to be known as the *resistance of growth.* Then, the work dissipated per unit mass in unit time is $P_d\dot{q}$, and if the modified function F_m assumes the form,

$$F_m = \tfrac{1}{2}\rho\dot{q}^2, \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{19}$$

as previously suggested by the evidence which points to the existence of H_d, we obtain from (18) and (19)

$$P_d \dot{q} = \dot{q} \frac{\partial F_m}{\partial \dot{q}} = 2F_m, \tag{20}$$

so that F_m itself is only one-half the time-rate per unit mass at which energy is *dissipated* into heat in connection with the transactions of growth. But since H_d is actually the full rate of dissipation per unit mass,

$$H_d = 2F_m. \qquad [\text{cal} \cdot \text{gm}^{-1} \cdot T^{-1}] \tag{21}$$

Finally, for the cases under consideration, F_m is evidently positive and ρ is likewise so.

The Heat of Synthesis, H_c.—From what has already been said about the two subtypes of motional heat represented by H_d and H_c in equation (9), it will be recalled that H_c exists, and is nonconservative, but that, unlike H_d, it is not truly dissipative in the dynamical sense. The latter means specifically that H_c cannot depend upon even powers of $\dot{q}$. Since H_d, on the other hand, does depend upon $\dot{q}^2$, and according to classical usage thus represents dissipativity, we propose to continue distinguishing between H_d and H_c as dissipative and nondissipative heat, respectively. But H_c, of course, is nonconservative because it represents a share of energy that cannot again be used by the organism; it has been suspected to be the part by which certain values of U (e.g., $U < A'$) must be accounted for; and it is finally kinetic because it has to do with growth in motion, and not with growth at rest. Its connection, however, with the process of cellular synthesis has not yet been stated.

Let us therefore consider, aside from the fact that $U \gtreqless 0$ does occur, the fundamental *physiological* need for such a term.

Had the possible existence of H_c not previously been mentioned, we should now be at the point of concluding that there is nothing in the form of equation (13) to prevent the remark that daughter cells, seemingly, make their visible appearance during self-multiplication after mere discharge from some concealed position in the surroundings, in which they would be supposed, accordingly, to reside fully *preformed*, much like shot in the magazine of a rifle. There is, to be sure, no evidence for such a state of affairs. Yet, even if quantitative data on the subject are at present wanting, there is at least sufficient accessory information to make it clear that daughter cells are *fashioned out of* raw materials provided by the source. This process of cell construction will evidently call for a corresponding outlay of energy, the work done being the work of *cellular synthesis*. Once accomplished through the agency of chemical reactions within the cells, this energy, or better, a portion of it not otherwise removed, will find a natural outlet by transformation into heat, else it too would be stored in the organism along with the basic building materials that ultimately constitute the body of the cell, of tissues, or finally of the organism. Thus, the work of synthesis may be expected to become manifest directly as heat. The indirect result of the actual work will be, among other things, the daughter cells themselves.

The foregoing characteristics of H_c as well as those which have already been mentioned in setting up equation (9) are consistent with the supposition that

(22) $$H_c = P_c\dot{q}, \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}]$$

where P_c is that part of the generalized impressed force P_g of equation (13) associated with the reaction of the system culminating in cellular synthesis. The form of P_c will be discussed in connection with that of P_g in the next section.

The Generalized Impressed Forces P_g and P_m.—The forces P_g and P_m have already been distinguished in (14) as generalized *external* and *net external* applied forces, respectively, and in view of (14) may be treated together. Now, just as P in the original equation of motion (10) does not possess the dimension of force unless ψ is a length, the term force being traditionally retained on the basis of mechanical analogy, so also are P_g and P_m to be considered forces in the generalized sense only. It is therefore perhaps preferable to define instead the quantities $P_g\delta q$ and $P_m\delta q$, which will have the dimensions energy per unit mass in view of the changes involved in replacing T in (10) with T_m, F with F_m, etc., in (11). In accordance with classical procedure they may be designated as the element of work done per unit mass by the respective *external* and *net external* forces in an arbitrary displacement δq of the coordinate q. Thus, since the coordinate q in the case of growth and hence the coordinate element δq are actually of zero dimensions, the forces P_g and P_m, if treated conventionally, will appear to have the same dimensions as the products $P_g\delta q$ and $P_m\delta q$, namely, *energy per unit mass*. While this should not give rise to any greater ambiguity than the suppression of an angle in exactly analogous examples among established physical quantities, it is possible to acknowledge the formal difference between the P's and the corresponding products, as we do in this paper, by including the symbol $[\text{q}^{\pm n}]$ with the appropriate numerical index ($n=1, 2, \cdots$) in the accompanying dimensional formulae. In this system of notation, the P's will then have dimensions $[\text{cal}\cdot\text{gm}^{-1}][\text{q}^{-1}]$, whereas those of the products, $P_g\delta q$, etc., will remain, as before, simply $[\text{cal}\cdot\text{gm}^{-1}]$. This procedure is suggested by, and is fully in accordance with, the recognized convention in the general mechanical case that P in (10) has the dimensions Energy/ψ.

We must now attempt to determine the *form* of these P's. To begin with, take P_m, for which any form consistent with the remaining conditions of the problem will do. There are, fortunately, some very significant events in growth that may be used as a guide in choosing a form of rather general application.

At this point let us again consider the kinematical nature of the general curve shown in Figure 1. It is readily understood that $P_m=0$ is a particular value which would suit the circumstances in the declining part of "phase" (a), and so also of branch (e_2); again, that $P_m=$constant is another particular value which would be consistent with the behavior of q in phases (b), (c) and (d) of Figure 1. We can, however, go much further than this, for the two different types of change illustrated by the branches (e_1) and (e_2), coupled with the fact, already stressed in discussing the curve in Figure 1, that growth is potentially periodic but ultimately degenerates into an asymptotic approach toward equilibrium, give us our most important suggestion as to a suitable and more general form for P_m. It is consequently pertinent to assume that P_m may be expressed as a damped harmonic function of the form,

$$P_m = \sum_{s=1}^{n} \epsilon^{-\beta_s t}(E_{m1}^{(s)} \cos \theta_s t + E_{m2}^{(s)} \sin \theta_s t) \tag{23}$$

in which the constants β_s and θ_s are not negative and the E's are either positive or negative constants. For ordinary cases it will be sufficient to use only two terms of this series. Then, by taking

$$\beta_1 = \theta_1 = 0,$$

$$E_{m1}^{(1)} = E, \quad E_{m1}^{(2)} = E_{m1}, \quad E_{m2}^{(2)} = E_{m2},$$

and letting

$$E_0 = \sqrt{E_{m1}^2 + E_{m2}^2}, \qquad \zeta = \tan^{-1} \frac{E_{m2}}{E_{m1}},$$

we may write, dropping the subscript 2 in β and θ,

$$P_m = E + E_0 \epsilon^{-\beta t} \cos(\theta t - \zeta) \tag{24}$$

for the net external generalized impressed force of growth.

The forces P_g and P_c may be expected to have the same form as that assumed in (23) and the same frequencies and damping constants β and θ. If so, we have,

$$\begin{cases} P_g = E_g + \epsilon^{-\beta t}(E_{g1} \cos \theta t + E_{g2} \sin \theta t), \\ P_c = E_c + \epsilon^{-\beta t}(E_{c1} \cos \theta t + E_{c2} \sin \theta t), \end{cases} \tag{25}$$

or

$$\begin{cases} P_g = E_g + E_{g12}\epsilon^{-\beta t}(\cos \theta t - \zeta_{g12}), \\ P_c = E_c + E_{c12}\epsilon^{-\beta t}(\cos \theta t - \zeta_{c12}), \end{cases} \tag{25'}$$

where, to take only the former,

$$E_{g12} = \sqrt{E_{g1}^2 + E_{g2}^2},$$

$$\zeta_{g12} = \tan^{-1} \frac{E_{g2}}{E_{g1}},$$

since similar relations exist among the E_c's. We also have,

$$\begin{cases} E = E_g - E_c, \\ E_{m1} = E_{g1} - E_{c1}, \\ E_{m2} = E_{g2} - E_{c2}, \end{cases} \tag{26}$$

when (24) and (25) are inserted into (14).

The Equation of Combined Activity in Determinate Form.—The results thus far obtained in equations (15), (17) and (19) may now be substituted into equation (13) along with the values of P_m, P_g, and P_c in (24) and (25). Then, since $\partial T_m/\partial q = 0$, we get, on rearranging terms,

$$\left[\lambda \frac{d^2q}{dt^2} + \rho \frac{dq}{dt} + \frac{q}{\kappa} - E - E_0\epsilon^{-\beta t} \cos(\theta t - \zeta)\right]\frac{dq}{dt} = M' - A', \tag{27}$$

where M' and A' in the general case are not necessarily constant or equal. But in the examples usually arising in practice, A', as already noted, will be constant for the species, and M' may likewise be taken so. In any case we shall obviously need to deal with the three particular conditions $(M'-A')\gtreqless 0$.

A solution of (27) for the cases $(M'-A')\gtrless 0$ has not been found in terms of a finite number of elementary functions. Integrating by series, we have, instead,

$$q = \sum_{j=0}^{\infty} a_j t^j, \tag{28}$$

where a_0 and a_1 are taken to suit the arbitrary boundary values of q and $\dot{q}$ at $t=0$, and where,

$$a_2 = \frac{(M' - A')\kappa - a_1[a_0 - \kappa(P_m - \rho a_1)]}{2\lambda\kappa a_1}, \tag{29}$$

the remaining coefficients of (28) being obtained in terms of the original constants in (27) by means of the recursion formula,

$$a_{(n+2)} = \frac{C_n\kappa - [\rho\kappa(n+1)a_{(n+1)} + a_n]a_1}{a_1\lambda\kappa(n+1)(n+2)}, \qquad (n = 1, 2, \cdots) \tag{30}$$

in which,

$$\left\{\begin{aligned} C_1 &= -\frac{(M' - A')\cdot 2a_2}{a_1} \\ C_2 &= -\frac{C_1\cdot 2a_2}{a_1} - \frac{(M' - A')\cdot 3a_3}{a_1} \\ C_3 &= -\frac{C_2\cdot 2a_2}{a_1} - \frac{C_1\cdot 3a_3}{a_1} - \frac{(M' - A')\cdot 4a_4}{a_1} \\ &\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots. \end{aligned}\right. \tag{31}$$

It may be remarked that the practical application of (28) with the coefficients given in (29) to (31) depends, aside from questions as to convergence for which reference may be made to Goursat (1924), upon knowledge of the numerical values of the constants in (27). This information, as we shall see in a succeeding section, may be obtained when data on heat production are available. As an example, consider the results elsewhere reported (Wetzel, 1934 *a*) on growth and heat production* following fertilization in *Bufo v.* based on observations by Gayda (1921) for which we may consider $M'=A'$, a case discussed more fully below. It has been found possible to compute a table for q with sufficient accuracy by employing only the first six terms of (28), the radius of convergence (see Knopp, 1928),

* Also given in Table 1 (p. 43) in connection with the corresponding curves in Figure 2 computed by means of equations (34) and (38) which imply $M'=A'$.

$$r = \frac{1}{\overline{\lim}\sqrt[j]{|a_j|}} \qquad (j = 1, 2, \cdots)$$

being approximately one-fifth to one-sixth of the entire growth interval. The table may then be extended by repeated application of (28).

While it is thus clear that (28) with the coefficients given above represents a solution of (27) for $M' \gtreqless A'$, we shall really need and use this solution only* in studying the effects of complete and partial starvation, two important physiological conditions for which $M' \neq A'$.

Far more frequently recurring, however, are the cases of normal or ordinary growth such as that just mentioned in which we have every reason to suppose that the rate M' at which maintenance energy is delivered per unit mass from the source is identical with the rate A' at which the associated heat of maintenance is liberated. It is true, of course, for many different organisms, that the ingestion of food is not wholly continuous with its actual utilization, the delay being consequent upon various intermediary processes of digestion; but it is equally true that we do not in practice need to regard this as a fundamental discrepancy, since we may, quite properly, accept the mean about which actual intake will fluctuate as the value for M', and likewise the mean value in any actual oscillation of maintenance heat output, as equal to A'.

If the foregoing point alone were at issue, we might perhaps dispense with the explicit mention of A' and M' in equation (27). But it is necessary again to emphasize that A' and M' are best retained in the indeterminate equation of activity (13), as well as in its determinate form (27), not only because they serve to align the analytical with the physiological conditions whereby both growth and maintenance are accounted for, but even more because we would otherwise be led into exceptionally serious errors when we come to deal with certain irregular situations, occasionally arising, that must be met by making the right hand side of (13) zero. This, in fact, occurs in the case of complete starvation which we shall treat briefly in later paragraphs.

The Equation of Motion in the Ordinary Case of Growth, $(M' - A') = 0$, and the Form of Φ.—From what has just been said it is clear that $M' = A'$ in normal ordinary examples of growth. Under these circumstances we have two possible cases consistent with the provisions of (27),

$$\frac{dq}{dt} = 0, \tag{32}$$

and,

$$\lambda \frac{d^2q}{dt^2} + \rho \frac{dq}{dt} + \frac{q}{\kappa} = E + E_0\epsilon^{-\beta t} \cos(\theta t - \zeta), \tag{33}$$

the former representing growth at equilibrium or rest, and the latter, the case of growth in motion within a neighborhood of equilibrium, $q = E\kappa$. Equation (33) thus determines Φ in (5).

* This, indeed, is the reason why it is not necessary fully to investigate the properties of (28) to (31) at the present time.

The complete solution of (33) for q at any time t may be written,

$$q = E\kappa + \frac{E_0\epsilon^{-\beta t}\cos(\theta t - \zeta + \xi)}{\sqrt{\left[\lambda(\beta^2 - \theta^2) - \beta\rho + \frac{1}{\kappa}\right]^2 + [2\beta\lambda - \rho]^2\theta^2}} + C_R\epsilon^{-\rho t/2\lambda}\sinh(\omega t + \gamma), \tag{34}$$

wherein,

$$\xi = \tan^{-1}\frac{(2\beta\lambda - \rho)\theta}{\left[\lambda(\beta^2 - \theta^2) - \beta\rho + \frac{1}{\kappa}\right]}$$

and,

$$\omega = \sqrt{\frac{\rho^2}{4\lambda^2} - \frac{1}{\lambda\kappa}}, \qquad \left(\frac{\rho^2}{4\lambda^2} > \frac{1}{\lambda\kappa}\right)$$

and where C_R and γ are the arbitrary constants of integration which can be evaluated in terms of λ, ρ, κ and two initial conditions usually involving q_0 and $\dot{q}_0$. Thus, for the case just cited in (34), ω real and not 0,

$$\begin{cases} C_R = \dfrac{1}{2\lambda\omega}\sqrt{(2B_2\lambda + \rho B_1)^2 - (2\omega\lambda B_1)^2} \\ \gamma = \sinh^{-1}\dfrac{2\omega\lambda B_1}{\sqrt{(2B_2\lambda + \rho B_1)^2 - (2\omega\lambda B_1)^2}} \end{cases} \tag{35}$$

where, for brevity,

$$\begin{cases} B_1 = q_0 - E\kappa - Q_0\cos(\xi - \zeta) \\ B_2 = \dot{q}_0 + Q_0\sqrt{\beta^2 + \theta^2}\cos\left(\xi - \zeta - \tan^{-1}\dfrac{\theta}{\beta}\right) \end{cases} \tag{36}$$

when, in turn, we let,

$$Q_0 = \frac{E_0}{\sqrt{\left[\lambda(\beta^2 - \theta^2) - \beta\rho + \frac{1}{\kappa}\right]^2 + [2\beta\lambda - \rho]^2\theta^2}}. \tag{37}$$

The solution for q given by equation (34) is in the form most commonly of use in practice, but cases also arise in which $(\rho^2/4\lambda^2) < (1/\lambda\kappa)$, so that ω is then imaginary, say, $\omega = i\omega_0$, and circular terms replace the hyperbolic expressions in (34) and (35).

It is beyond the scope of the present paper to discuss in detail all of the interesting relationships between the constants in these equations, or to analyze fully the effects that are to be expected when special values are assigned to them.

We confine our attention to the chief properties which equations (33) and (34) along with the expressions (35) and (36) most clearly exhibit.

Remarks on Equations (33) *and* (34).—The generalized component of impressed force on the right of (33), as given by the approximation for P_m in (24), consists of two parts, a constant term E, and a damped harmonic function of the time with the coefficient E_0. Each of these gives rise in (34) to two corresponding components among the three major parts of which q is composed. The third portion, represented by the hyperbolic term, is associated with the three fundamental kinds of energy transformation discussed in connection with the formulation of the functions T_m, F_m, and V_m. The last term of (34), accordingly, is the "free" oscillation which the system would display when left to itself in the absence of any impressed force of growth, *i.e.*, when $E=E_0=0$.*

The resultant oscillation of q then is doubly periodic, so long as $E_0 \neq 0$, the free oscillation in the case described above having the imaginary period $2i\pi/\omega$ since ω is real, and the harmonic part of the forced oscillation having the period $2\pi/\theta$. When $\omega = i\omega_0$, as already noted, both periods are, of course, real. It is, clearly, of interest that the *frequency* of the forced oscillation in (34) is precisely the frequency of the applied force P_m in (33), and that it is entirely independent of the characteristics of the system denoted by ρ, λ, κ; the forced *amplitude* Q_0, however, is dependent not only upon the three latter constants but upon the damping factor β, and the angular velocity θ as well. Both oscillations, moreover, are damped, the forced oscillation by β, and the free oscillation by the coefficient $\rho/2\lambda$. If β is large, the harmonic component dies away rapidly and subsequent oscillation is then due entirely to the free component represented by the complementary function in (34). This, too, ultimately dies away, and the system approaches ever more closely to the steady state represented by $q = E\kappa = q_f$, some position of stationary equilibrium. The larger κ, the higher the ultimate level $E\kappa$ will be with respect to $q=0$, and it is on this account that κ is termed the permittance of growth.†

Thus it is evident that the solution for q as given by (34) appears to be wholly consistent with the various trends of the curve in Figure 1. But it is also plain that all of the kinematical characteristics therein displayed could not be represented by an equation containing, say, only two of the three main terms in (34), although considerable portions of the curve could be represented either by the

* This condition, however, must not be confused with that of complete starvation later to be discussed.

† Compare what has been said in connection with the positional properties of growth (page 26) with the fact that the equilibrium level q_f now turns out to consist of the product of the two parts E and κ. The significance of these relationships is beautifully brought out in Richards' results cited previously, for (33) in his case of yeast growth becomes simply $\rho\dot{q} = E - q/\kappa$, the equilibrium position in the control tubes being again $E\kappa$. By changing the culture medium at more and more frequent intervals (removing accumulated alcohol, the chief inhibitor of yeast growth) $q/\kappa \to 0$ and $\dot{q}$, instead of diminishing with increase in time, as in the controls, approached and remained equal to E/ρ, that is, the rate of growth at the beginning of the experiment when q itself was still small compared with $E\kappa$, and hence, equal to the rate which the medium could naturally support. Since q increased greatly as a result of the experimental procedure and since $\dot{q}$ did not exceed E/ρ, it is clear that the net effect must have been one to increase the permittance κ.

sum of the first and second, or first and third terms in (34) if the problem were viewed simply as one in curve fitting.

It is well to emphasize again that the application of (33) and (34) to data on growth actually implies the several following physiological conditions, each corresponding to an analytical condition which equation (27) must satisfy: (*i*) that the organism, as initially postulated, is continuously in contact with a suitable source of energy which provides those substances necessary to growth as well as to maintenance; this means that E and M', at least, in (27) are different from zero and in the usual case of ordinary growth, positive, so that $E_g > E_c$; (*ii*) that the organism can utilize this supply, in which case ρ, λ, κ, E and A' cannot all be zero; and finally (*iii*) that energy for maintenance is utilized as rapidly as it is supplied, or that $(M'-A')=0$. The latter condition is especially important since (34) is not an integral of (27) when $(M'-A') \gtrless 0$. For all such cases, however, we revert to (28).

Applications to Actual Experimental Data on Ordinary Growth

Since the solution of (33) as given by (34) is seen to be capable of representing the kinematical features displayed by the curve in Figure 1, we may be prepared to apply (34) to any particular example of growth for which suitable experimental data can be found.

At this point it may be remarked that we are interested in the matter of curve fitting only to the extent of bringing forward tangible evidence to show, in the first place, that a wide variety of observations on normal growth conform to the provisions of equation (34). This, in fact, is the only method at present available by which the implications of the modified Lagrangian equation of activity (13) can be put to test. But in order to offset any limitations which proof of this kind might be thought to possess, we shall also have the occasion to remark that the associated events of heat production can be satisfactorily represented by the portion U in equations (13) and (27). We shall finally note that the theoretical results to be expected when $M'=0$ in (27) are in entire accord with actual experimental data on loss in weight as well as on heat output during complete starvation in adult human subjects.

If, then, data on ordinary growth itself can be represented by q in (34), the corresponding data on heat output by U, and the case of starvation by (28) and (9), the presumption will be that we have proved, so far as is now possible, the admissibility of equation (13) to the problem of growth, and, in consequence of the developments leading to (34), that the motion of growth is intrinsically dynamical, or better perhaps, that it belongs to the nonconservative dynamical phenomena in nature.

We need not here go through the actual steps of demonstrating the application of (34) to data on ordinary growth (i.e., when $M'=A'$), for pertinent examples of this have already been reported in earlier papers (Wetzel, 1932–33, 1934 *a*, *c*). We may, however, briefly recall that (34) has been applied to, and has been shown to hold with remarkable fidelity in, widely differing cases that include measurements of growth in unicellular populations such as bacteria,

yeasts, tissue cultures, and protozoa on the one hand, as well as observations on growth in multicellular organisms on the other hand. Among the latter, special mention must be made of the results which (34) gives in the case of the developing tadpole, the domestic fowl, and in the human case, because data on simultaneous heat production are likewise available in each of these three instances. In each, moreover, equation (34) holds for the embryonic as well as for the postembryonic and postnatal periods of existence. The range throughout which it represents the trend of events in these examples of growth is thus very extensive, as is shown, for instance, in the case of *Bufo vulgaris*, illustrated graphically by the curves for q and z in Figure 2, the numerical values of the constants in equations (33) and (34) being given in Table 1.

In addition to the foregoing selected cases we have also tested (34), or one of the simpler forms into which (34) degenerates under certain conditions, for instance when E_0 or λ is negligibly small, in examples of growth for which no data on simultaneous heat production are as yet available (Wetzel).* These include the embryonic and postnatal periods of growth in the rabbit, guinea-pig, and mouse, as well as the postnatal epochs in various larger animals and birds. The results, judged not only by the eye, but also by various methods of goodness of fit, wherever applicable, are again all that could be expected when the natural variability of biological material as a whole, and the variation in individual observations are taken fully into account.

It is important to note that (34) has thus been shown to apply to the more complicated episodes of growth which begin with the earliest measurable stages in the embryo and include the continuous succession of events throughout the entire remaining span of life. In other words, the application of (34) has not been confined to short and arbitrarily chosen segments of individual growth curves; instead, the attempt has been made to obtain the fullest possible degree of corroboration in every example thus far studied so that we might deal effectively, as here in Figure 1, with a very general, if not with the most general case of growth.

One of the indirect yet no less important consequences of dealing comprehensively with growth as a continuous event throughout the life of an organism is exemplified in the human case where the detection of a minimum in $\dot{z}$ as well as in $\dot{q}$ between the third and fourth postnatal years has led to the suggestion (Wetzel, 1934 *c*) that adolescence actually begins where infancy leaves off, namely, at 3.30 years, the junction between the circumnatal and adolescent epochs of life. The corresponding curves of heat production, discussed in the next section, likewise considered as a continuous and life-long phenomenon, show trends that are strikingly in support of this view, for which, indeed, a considerable body of evidence on human physical development can also be brought forward.† These results, to be sure, pertain directly to the earlier years of life;

* To be published.

† Boyd, working in Scammon's laboratory, has presented further evidence in her treatise (1935) on the surface area of the body in favor of the view referred to above that the human developmental period consists of two distinct epochs, the circumnatal and the adolescent, and, accordingly, agrees that adolescence extends from about 3 years to maturity.

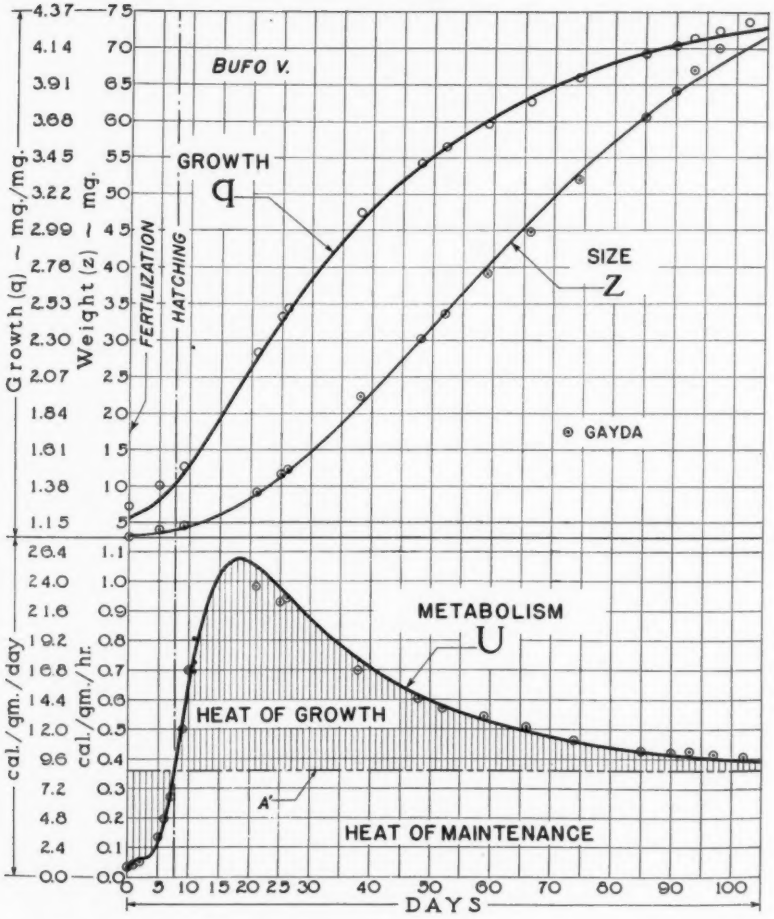

FIG. 2. The curves of growth, cumulative gain in weight, and of heat production, q, z, and U, respectively, in the case of the amphibian, *Bufo vulgaris*, as computed from equations (34), (4) and (38), with the help of the constants in Table 1. The dotted circles represent Gayda's (1921) experimental values. The solid circles centered at the twenty-second hour of the tenth day illustrate the scatter of his three groups of observations made during the first eleven days following fertilization.

The adjustments are as satisfactory as could be hoped for, if due account be taken of the errors inherent especially in biological measurements. The magnitude of the probable errors of unit weight and the precision of the constants in Table 1 give numerical corroboration of the visible goodness of fit and speak unmistakably for the superlative character of Gayda's original observations.

Many of the characteristics discussed in connection with the properties of systems undergoing growth are exhibited here. Note particularly the trend in U, e.g., in the early stages where $U < A'$ and compare with text in connection with equation (9). The rise, the fall, as well as the peak exhibited by U in the figure, depend, in view of (38), explicitly on the rate of growth.

but similar suggestions are to be found at a later age where the final point of inflexion in $\dot{q}$ coincides precisely with the onset of puberty which may, therefore, be quite easily recognized to be an episode in, rather than a period coextensive with, an otherwise loosely demarcated epoch of adolescence.

TABLE 1*

THE NUMERICAL VALUES OF THE CONSTANTS IN EQUATIONS (33), (34), (35) AND (38) FOR THE CASE OF *Bufo vulgaris* ILLUSTRATED IN FIGURE 2

$\rho = 2404 \pm 70$ cal. day gm.$^{-1}$ q^{-2}	$E_{m1} = -243.40$ cal. gm.$^{-1}$ q^{-1}
$\lambda = 13900 \pm 2100$ cal. day^2 gm.$^{-1}$ q^{-2}	$E_{m2} = 101.47$ cal. gm.$^{-1}$ q^{-1}
$\kappa = 0.01740 \pm 0.00081$ gm. cal.$^{-1}$ q^2	$E_K = 4.478 \pm 0.077$ q
$E = 257 \pm 13$ cal. gm.$^{-1}$ q^{-1}	$A' = 8.646 \pm 0.050$ cal. gm.$^{-1}$ day^{-1}
$E_0 = -263.71$ cal. gm.$^{-1}$ q^{-1}	$C_R = -3.74 \pm 0.14$
$E_c = 123.9 \pm 4.1$ cal. gm.$^{-1}$ q^{-1}	$\gamma = 0.824 \pm 0.048$
$E_{c1} = -516.7 \pm 8.8$ cal. gm.$^{-1}$ q^{-1}	$\beta = 0.248$ day^{-1}
$E_{c2} = -1470 \pm 33$ cal. gm.$^{-1}$ q^{-1}	$\theta = 0.1434$ day^{-1}
$E_{c12} = -1558 \pm 31$ cal. gm.$^{-1}$ q^{-1}	$\zeta = -0.39498$
$E_g = 381 \pm 14$ cal. gm.$^{-1}$ q^{-1}	$\zeta_{c12} = (\pi/2) - 0.3381 \pm 0.0088$
$E_{g1} = -760.12$ cal. gm.$^{-1}$ q^{-1}	$\xi = 1.52433$
$E_{g2} = -1368.18$ cal. gm.$^{-1}$ q^{-1}	$\omega = 0.0579 \pm 0.0098$

The P.E.'s of a single observation:

q,	$\pm$ 0.017 mg./mg.
z,	$\pm$ 0.049 mg.
(Weighted for number of organisms)	$\pm$ 0.35 mg.
U,	$\pm$ 0.020 cal./gm./hr.

* Standard methods as described by Whittaker and Robinson, Brunt, Runge and König, and by Scarborough have been employed throughout the computations for q, z and U; for the corresponding probable errors "of a single observation" likewise given in the table, as well as for the P.E.'s of the constants themselves. For various reasons the errors of some constants could not be calculated and these are tabulated to the five or six figures used in computing the values for the curves. Special attention, however, has been given to the matter of including all cross-products in calculating the errors of certain constants which are functions of those whose own P.E.'s had been obtained from the coefficients of the normal equations. Of the fifteen constants in the table for which P.E.'s are given, thirteen are between 17 and 170 times larger than their own errors and are thus significant. Even the two most poorly determined constants, λ and ω, are likewise statistically significant, since they turn out to be about 6 to 7 times larger than their own P.E.'s.

The unitalicized symbol $q^{\pm n}(n=1, 2)$ included in the units in which the constants are expressed does not represent the quantity of growth q as defined by equation (4), but rather its dimensions, as explained in the text.

The seemingly great number of constants tabulated here may recall a common misunderstanding. It is rather widely understood and thus remarked upon in situations of this kind that any set of observational data, however complex, may quite readily be represented by "an equation" if a sufficient number of constants be introduced into it, which is unfortunately thought to be equivalent to the statement that any continuous function of the variables can be approximated to any desired degree of accuracy by a suitably chosen polynomial, or more generally, by an interpolation series. The objection thus intended does not, accordingly, apply to (34), which is the equation in the present case that is to be applied or fitted to the data, even in spite of the fact that the part of (34) representing the "forced oscillation" (see text) is actually given by the first two terms of the series for P_m in (23). Equation (34), in other words, is not an interpolation formula and hence is not subject to the foregoing criticism. The constants which it contains, however numerous they appear, are actually present in the preceding differential equation (33), but, more important still, in equation (13), which takes the fundamental properties of growth and maintenance, represented by T_m, V_m and U explicitly and fully into account. These three reactions on the part of the system imply, on general dynamical theory, that P_m and hence, if the form of (23) be appropriate, that the E's, as well as β and θ, actually exist. The constants in (34) thus do not outnumber the specific properties with which we find it necessary to deal in attempting a dynamical analysis of organic growth.

Considering, then, the successful applications of equation (34) to the widely differing circumstances of growth among the organisms just mentioned, we are in position to understand that this common biological heritage may provisionally be placed in the class of natural dynamical phenomena. Further substantiation of this view, so far but partly established by the afore-mentioned adjustments to data on growth alone, is to be obtained from the results we shall next describe in connection with the associated nonconservative reactions of energy transformation into heat.

Applications to Heat Production Accompanying Ordinary Growth

Since the indeterminate equation of activity (13) contains F_m and H_c, it is clear that, so long as ρ and $E_c \neq 0$, the determinate equation of motion (33) and its integral (34) must likewise take some account, however indirectly expressed, of heat that is traceable to growth itself. Hence the relationship between heat production during growth and the quantity of growth itself is merely implicit in (34) and it is to be recognized simply by the various ways in which ρ and E_c enter into the several terms of (34).

A satisfactory application of (34) to data on growth thus means that the properties represented by T_m, V_m, and U are thereby presumptively even if indirectly established. In the absence of any means of measuring the physical entity to which F_m, for example, refers, we should be required to leave the matter at this point; but, since heat output can be measured, we are obliged to consider the explicit relationships between growth and heat production, and we may actually profit by the advantage of studying U directly. This, obviously, is of great importance on its own account, and the results will add materially to the evidence already introduced in connection with the application of (34) to experimental data on growth.

In order to apply equation (9) for composite heat output U to actual data on heat production, it is now only necessary to substitute the values for $2F_m$ and H_c which may be obtained with the help of equations (19), (21), (22) and (25) into (9), whereby,

$$(38)\quad \begin{cases} U = 2F_m + P_c\dot{q} + A' \\ \quad = \rho\left(\dfrac{dq}{dt}\right)^2 + \left[E_c + E_{c12}\epsilon^{-\beta t}\ \cos(\theta t - \zeta_{c12})\right]\dfrac{dq}{dt} + A' \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \end{cases}$$

in which,

$$E_{c12} = \sqrt{E_{c1}^2 + E_{c2}^2},$$

$$\zeta_{c12} = \tan^{-1}\frac{E_{c2}}{E_{c1}},$$

so that the amplitude E_{c12} and the phase constant ζ_{c12} are expressed in terms of the amplitudes of P_c in (25).

Since dq/dt, β, and θ will have been determined in the application of (34) to

data on growth, it will be possible to evaluate ρ, E_c, E_{c12}, ζ_{c12} and A' by adjusting (38) to the corresponding data on heat production.

As in the case of equation (34) and its application to observations on growth, it is unnecessary here actually to describe the results which have been obtained in testing (38) against available experimental data on heat production, for these have been reported elsewhere. It may be stated, however, that (38) or its integrals have been applied to the case of heat production in bacterial cultures (Wetzel, 1932–33 *f*); to heat output in the amphibian *Bufo v.** over the rather extensive period of its development beginning with fertilization of the egg and ending with metamorphosis some 100 days later (Wetzel, 1934 *a*); to the entire embryonic and post-hatching epochs in the chick and domestic fowl (Wetzel, 1934 *b*)†; to the earliest stages of growth just immediately following fertilization of the Echinoderm egg‡; to the postnatal data on heat production in cattle, horses, swine and sheep‡; and, finally, to the data on heat production in man from birth to full maturity (Wetzel, 1932–33 *c*; 1934 *c*). The trend of known changes in heat production with advancing age is faithfully represented by equation (38) or by the simpler form into which it degenerates when E_c or E_{c12} is very small, in each of the examples just mentioned; but, as is always to be expected, the adjustments of (38) are more satisfactory wherever the original data are more precise and show less scatter among individual observations.

The significance of these results is appreciably increased by recalling that $\dot{q}$, β, and θ cannot be arbitrarily chosen for the adjustment of (38) to data on heat output during growth. For the three quantities just mentioned are fixed when (34) is applied to the data on growth, and it is therefore evident that their presence in (38) actually has the effect of imposing severe restrictions upon the application of the latter equation to data on heat.

The foregoing results may therefore be taken to establish the experimental validity of (38) as far as existing data on normal growth and heat production are concerned. We may, accordingly, look upon (38), since it gives U in terms of $\dot{q}$, as the explicit connection between the events of growth on the one hand, and the concomitant phenomena of heat production during growth, on the other hand.

It seems fair to say that many curious changes occurring in growth and in heat curves warrant reinvestigation, and that more satisfactory explanations of them might be forthcoming if they could be studied with the analytical relations between the various terms in equation (38) itself in mind, or, better, in the light of the entire development that takes its origin in the modified Lagrangian equation of activity (13) and culminates up to this point in (34) and (38).

Thus, of several possible methods of testing the validity of the general equation (13), we have now completed two: (*i*) the demonstration that the integral (34) satisfactorily represents data on growth, q; and (*ii*) the alternative method of directly checking the implications of F_m through the medium of U in (38). Similar direct checks might have been applied in respect of T_m and V_m in (13)

* See Fig. 2 and Table 1.

† Preliminary presentation; to be published in full.

‡ To be published.

if we possessed a means of measuring the effects of inertia and of position much as a portion of the heat output has now been seen to measure the effect of F_m. Substantiation of T_m and V_m is not, however, entirely wanting because the ultimate effects arising out of T_m and V_m are actually represented, though indirectly so, by λ and κ, respectively, in every case of growth that conforms to (34).

Topics Related to the Work of Growth

The External Work of Growth and Its Various Components.—The opinion has been expressed from time to time that Tangl's conception (Tangl, 1903; Tangl and Mituch, 1908) of what he called "Entwicklungsarbeit" is not well founded, at least not so far as observations of energy exchange in the developing chick embryo are concerned (see Needham, 1925, 1931). It is contended, instead, that growth in this case proceeds, to be sure not without expenditure of energy supplied by the yolk, but rather without the corresponding appearance of equivalent work done, for the existence of a work of growth is questioned on the ground that the quantity of energy originally in the egg can be entirely accounted for when the fuel value of the hatched chick and its membranes as well as the heat liberated during incubation are added to the fuel value of the residual yolk at hatching.

A study of this important question by the methods of the present theory shows, however, that Tangl's "Entwicklungsarbeit"* for the twenty-one day period of incubation is quantitatively identical with

$$\int_0^{21} (Uz)dt + x, \qquad \text{[cal]} \tag{39}$$

where x is the all but negligibly small† portion of heat liberated by the membranes themselves. Comparing this result with the dimensionally equivalent expressions that may be obtained with the help of (15) and (17) from equation (13) by multiplying the latter by mass z, and integrating the products with respect to time, we are clearly in position to see that Tangl's quantity actually represents work of a dual character because (39) is part of the *combined* work of growth and maintenance,

$$\int_0^t z[P_\varphi \dot{q} + M']dt \equiv \int_0^t z\frac{d}{dt}(T_m + V_m)dt + \int_0^t (Uz)dt, \qquad \text{[cal]} \tag{40}$$

and we may conclude that it does deserve to be considered in the sense of work. Indeed, from the present developments, it would appear legitimate to state not only that a work of growth as such exists, but also that this may actually be represented by the portion,

* 22,940 gm. cal.

† The quantity x represents approximately 1880 gm. cal. as computed from recent data by Needham (1932).

$$\int_0^t zP_g\dot{q}dt \equiv \int_0^t z\frac{d}{dt}(T_m + V_m)dt + \int_0^t (2F_m + P_c\dot{q})dt, \qquad [\text{cal}] \tag{41}$$

in (40), provided, again, that $M' = A'$. Now (41), according to the distinctions already made between P_m and P_g in (14), is really the *external* work of growth. The second integral on the right of (41) will be recognized from (38) as that part of the work of growth which appears in the form of heat. The other part on the right of (41), which depends on the kinetic and positional properties T_m and V_m, respectively, and which, accordingly, is identical with

$$\int_0^t z\left[\lambda\ddot{q} + \frac{q}{\kappa}\right]\dot{q}dt, \qquad [\text{cal}] \tag{42}$$

we shall call the *reactive* work of growth, for reasons appearing in the next section.

Combined Growth-Maintenance Power per Unit Mass.—In place of (40) it is more appropriate for many purposes to express the combined work of growth and maintenance in terms of power per unit mass. This, moreover, may be represented explicitly as a function of time t, if we replace $\dot{q}$ on the right of (13) by the value of the first derivative of (34), whence, if the result be denoted by W_{GM},

$$\begin{aligned} W_{GM} &\equiv (P_g\dot{q} + M') \\ &\equiv [E_g + E_{g12}\epsilon^{-\beta t}\cos(\theta t - \zeta_{g12})]\left[\frac{C_R\epsilon^{-\rho t/2\lambda}}{\sqrt{\lambda\kappa}}\sinh\left(\tanh^{-1}\frac{2\omega\lambda}{\rho} - \omega t - \gamma\right)\right. \\ &\quad \left. - Q_0\sqrt{\beta^2 + \theta^2}\epsilon^{-\beta t}\cos\left(\theta t - \zeta + \xi - \tan^{-1}\frac{\theta}{\beta}\right)\right] + M', \end{aligned} \tag{43}$$

the value of P_g being taken from the first of equations (25)′. Equation (43) shows that energy actually must be expected to surge between the organism and the source as long as t is not too great. This, indeed, is not at all without experimental support, for certain observations on the migration of glucose in and out of the developing chick embryo (Needham, 1927–28), as well as older data on heat production in the same organism (Bohr and Hasselbalch, 1903), may now be viewed as evidence, at least presumptively, in harmony with the foregoing results.

But the effect of damping will eventually diminish the energy for growth to negligible amounts, and the supply W_{GM} of (43) will then remain constant, equal to M', and will provide only for the purely nutritional demands of cell maintenance. This, of course, is consistent with the facts of general experience that ordinary growth comes sooner or later to a close, and that consumption of energy is meanwhile correspondingly reduced.*

If β is comparatively large, (43) will become simply

$$W_{GM} = M' + \frac{E_gC_R}{\sqrt{\lambda\kappa}}\epsilon^{-\rho t/2\lambda}\sinh\left(\tanh^{-1}\frac{2\omega\lambda}{\rho} - \omega t - \gamma\right), \tag{44}$$

* Under basal conditions to the maintenance level.

and power will flow unidirectionally from source to organism unless, as sometimes happens, ω is imaginary, in which case, power will again surge to and fro between the source and the organism until this oscillation of energy has been abolished, for practical purposes, through the effect of increasing values of t in the exponential factor. Thereafter, absorption and supply of energy will again consist of the quantity M' only, which, as we have seen, will be transformed into the corresponding heat of maintenance, A'.

The foregoing possibility of oscillation in power thus depends on the condition that,

$$\left(\rho^2 - \frac{4\lambda}{\kappa}\right) < 0.$$

Since λ and κ are associated with T_m and V_m, respectively, it is convenient to refer to the item given by (42) as the reactive work of growth as opposed, for example, to the work appearing as heat which is associated with (F_m+H_c).

The Energy Content of the Organism

Thus far no explicit account has been taken of the energy contained in the immediate bodies of organisms although this quota must likewise be delivered by the source. In the strict sense it could not be construed as work; it is rather to be conceived as the energy equivalent of the corresponding raw materials once residing at the source, which have been fashioned into protoplasm, the latter, in turn, being *organized* into cells and tissues such as flesh and blood, at the expenditure involved in, and represented by, the combined work of growth and maintenance in (40).

By methods similar to those already employed in dealing with the question of maintenance and synthesis, it is possible to provide for this additional quantity of energy which appears in the substance of the organism. In fact, if S be the power per unit mass delivered by the source not only to meet the needs represented by the combined work of growth and maintenance, W_{GM} in (43), as previously described, but to supply the energy contained in the raw materials of protoplasm, $R\dot{q}$, as well, we have,

$$(S - R\dot{q}) = (S_G - R)\dot{q} + M' = W_{GM}, \tag{45}$$

where $(S_G\dot{q})$ is the power per unit mass delivered for all requirements except maintenance, M'. As before, we assume, for the general case,

$$\begin{cases} R = R_c + \epsilon^{-\beta t}(R_{c1}\cos\theta t + R_{c2}\sin\theta t), \\ S_G = S_g + \epsilon^{-\beta t}(S_{g1}\cos\theta t + S_{g2}\sin\theta t), \end{cases} \tag{46}$$

the R's and S's on the right being constants. We thus get from (13),

$$\left[\frac{d}{dt}(T_m + V_m)\right]\dot{q} + U = \left\{(S_g - R_c) + \epsilon^{-\beta t}\left[(S_{g1} - R_{c1})\cos\theta t + (S_{g2} - R_{c2})\sin\theta t\right]\right\}\dot{q} + M', \tag{47}$$

which is really equivalent to (27), since,

$$(48) \qquad \begin{cases} (S_g - R_c) = E_g, \\ (S_{g1} - R_{c1}) = E_{g1}, \\ (S_{g2} - R_{c2}) = E_{g2}, \end{cases}$$

on comparing (47) with the first identity in (43). Unfortunately, however, the only data in existence by which the full implications of (45) and (47) can at present be tested are those on the developing chick embryo, and even here it is necessary to use the results of several workers (Murray, 1925–26; Byerly, 1932; Needham, 1932) whose observations have been made on specimens of different incubation age, on different breeds of chick, or by entirely different methods. In spite of these severe restrictions it has nevertheless been possible to obtain wholly encouraging corroboration of this point. Thus, in the final accounting, the sum of all terms in the corresponding integral of energy over the twenty-one day period,

$$(49) \qquad \int_0^t (R\dot{q} + W_{GM})zdt,$$

when added to the known values (Tangl, 1903; Fauré-Fremiet, 1925) for energy represented in the extra-embryonic membranes themselves, in their own respiration, and in the residual yolk supply at hatching, gives a result that is remarkably close to the accepted values for the energy content of the hen's egg (Wetzel, 1934 *b*).* We may, accordingly, regard this as the third bit of evidence which, together with the results on growth itself and those on heat production, already mentioned, is strongly in favor of various implications that can be discerned in equations (13) to (47).

Motion in Systems Completely or Partially Deprived of Normal Sources of Energy

Up to this point we have treated only the case of motion in systems supposed to be continuously supplied with energy, both sufficient as well as suitable, for growth and maintenance of the organism. We shall finally consider the course of events that may be expected, on present theory, to take place when this usual state of affairs is disturbed by depriving an organism of its normal food supply. The results will be seen to agree with existing experimental data on complete and partial starvation and they will thus afford evidence of quite different character than before in support of the general implications of equations (13) to (38).

Complete Starvation; The Condition $S_G = M' = 0$.—In complete starvation no energy in the form of food is supplied from outside sources. This conforms to the particular condition, $S_G = M' = 0$, in equation (45). We then have, upon rearranging (47) in descending powers of $\dot{q}$,

* Preliminary presentation; to be published in full.

$$\rho\left(\frac{dq}{dt}\right)^2+\left\{\lambda\,\frac{d^2q}{dt^2}+\frac{q}{\kappa}+(R_c+E_c)+R_s\epsilon^{-\beta(t_s+\tau)}\cos\left[\theta(t_s+\tau)-\zeta_s\right]\right\}\frac{dq}{dt}+A'=0, \tag{50}$$

where,

$$R_s=\sqrt{(R_{c1}+E_{c1})^2+(R_{c2}+E_{c2})^2},$$

$$\zeta_s=\tan^{-1}\frac{R_{c2}+E_{c2}}{R_{c1}+E_{c1}},$$

if time τ now be reckoned from the moment t_s at which fuel is discontinued. This event is quite accidental and may obviously take place at any point along the t-axis of the general curve $q=\phi(t)$ in Figure 1. Equation (50), it may be noted, has the same form as (27).

The constants ρ and A' are again to be considered positive, and the roots of (50) if real will therefore both be negative when, as most frequently happens, the bracketed coefficient of $\dot{q}$ is also positive. If, however, $\ddot{q}$ or the harmonic term, either alone or in combination, is negative and greater than $1/\kappa[q+(R_c+E_c)\kappa]$ at t_s, both roots will be positive so that the general case for real roots represented by (50) includes the possible case of a temporary increase in q in spite of the actual removal of a normal source of energy.

The application of (50) presents some difficulties. If, for example, starvation be instituted in young organisms, that is, when t_s is not large in comparison with t_0, the original onset of growth, it will be necessary to retain all of the terms in (50), the general solution of which will have the form given by (28). There are, however, no suitable data by which the results can be satisfactorily checked. Nevertheless it is worth remarking that acute starvation in infants (t_s small) may be expected, from the dynamical point of view, to be more serious than in fully mature adults (t_s large). For, other things being equal, $(-\dot{q})$ will be greater if t_s is small enough to require that the harmonic term be retained, than it will be if this term can be neglected, that is, when t_s is large, and hence, when an organism has advanced into the stationary state $[q=q_s;\ \dot{q}=0;\ \ddot{q}=0]$.

In the latter case, we have, without great loss of generality,

$$\rho\left(\frac{dq}{dt}\right)^2+\left[\lambda\,\frac{d^2q}{dt^2}+\frac{q}{\kappa}+(R_c+E_c)\right]\frac{dq}{dt}+A'=0, \tag{51}$$

it being understood that time t will again be reckoned from the new origin t_s, and that $\tau=(t-t_s)$. Unless $\ddot{q}$ is negative and comparatively large, the roots of (51), like those of (50), will also both be negative so that q, and hence z, will decrease as τ increases. The complete solution of (51) for q in terms of t will be given by (28) so long as $\lambda\ddot{q}$ and A' must both be retained. Owing to the fact that the primary physiological demands of maintenance must always be provided for, and because these cannot, accordingly, be avoided in any living organisms,

it will never be possible to neglect A' in (51). But the case $\lambda\ddot{q}\to 0$ does arise and we shall treat it in the course of some alternative procedures.

To begin with, we form the first integral of energy, which may be written,

$$(52)\quad \frac{\lambda}{2}\left(\frac{dq}{dt}\right)^2+\frac{q^2}{2\kappa}+R_cq+\rho\int_{\tau=0}^{\tau}\left(\frac{dq}{dt}\right)^2dt+E_c(q-q_s)+A'\tau=\frac{q_s^2}{2\kappa}+R_cq_s,$$

time being reckoned from $\tau=0$, and $[E_cq_s+(q_s^2/2\kappa)+R_cq_s]$ representing the constant of integration which is evaluated from the facts that at t_s, $q=q_s$, and that heat output at the same instant is zero. Thus, the right hand side represents the quantity of energy per unit mass for growth q_s which the organism has previously accumulated up to the moment t_s. This consists, in part, of the potential energy per unit mass, $(q_s^2/2\kappa)$, and, in part, of the energy per unit mass accounted for by the fuel value (R_cq_s) of the raw materials in the protoplasm of the organism. These two portions together afford the sole source of energy for the work required, at least temporarily, by the continued existence of the organism. The energy represented by $(-E_cq_s)$ has been liberated previous to t_s in the form of heat. It is written on the left of (52) to show that the heat of synthesis, $E_c(q-q_s)$, like that arising from dissipation, as well as like that from maintenance, is zero at t_s.

Now, since the right hand side of (52) is constant, the left hand side must likewise remain so; hence, the sum of the first three terms, which, on comparing with equation (47), we see to be energy associated with the organism as such, must decrease as time advances, in contrast to the evidently continuous increase in the second three terms which represent energy transformed into heat. Thus, it is again clear that q will decrease as t increases, and, if λ and ρ are small compared with $1/\kappa$, R_c, E_c, and A', that q^2 as well as q itself will tend to decrease linearly as a result of the continued demands of maintenance represented by A'. Both of these results are in harmony with actual data on prolonged fasting in mature rats, pigeons, guinea-pigs and men.

When, however, the effect of the inertia term predominates over that of the other terms in q or $\dot{q}$, as is most likely to be the case immediately after the original condition of equilibrium has been disturbed by sudden removal of food, we find instead that $\dot{q}^2$ will fall off almost linearly, in accordance with,

$$(53)\qquad \left(\frac{dq}{dt}\right)^2=-\frac{2A'}{\lambda}\tau+C_q,$$

since C_q, which is taken to represent all other terms in (52) will then remain approximately constant, because the increase in the dissipation integral will tend to offset the accompanying decrease of q in the associated terms contained in C_q.

It is interesting that the nearly linear condition in (53) is surprisingly well exhibited by data during the initial stages of human fasting. This, however, can only be temporary, that is, until

$$\tau = \frac{C_q \lambda}{2A'}, \tag{54}$$

for $\dot{q}^2$ thereafter becomes negative and $\dot{q}$ itself imaginary. The critical value for τ in (54) turns out to be about 8.6 days following the onset of complete starvation in Benedict's (1915) subject Levanzin, the descent of $\dot{q}^2$ being almost exactly linear until as late as the seventh day. The value for λ thus computed from applications of (53) to human data during the initial stages of starvation is in good agreement with those obtained by applying the complete first integral (52) to the data for the entire period of inanition. Thus, in the early stages,

$$q = \frac{\lambda}{3A'}\sqrt{\left(C_q - \frac{2A'}{\lambda}\tau\right)^3} + C_0, \tag{55}$$

wherein C_0 is arbitrary, so that the curve for q itself is concave upwards during the early stages of complete starvation. These results may thus be interpreted to mean that maintenance during the early stages of inanition has been chiefly supplied by the kinetic energy of (negative) growth. The exhaustion of the latter source implies that $\lambda\ddot{q}\dot{q} \to 0$, from which $\ddot{q} \to 0$, since neither λ nor $\dot{q}$ can be zero by (51). Thus, $\ddot{q}$ will at last become negligible in (51), however large λ may happen to be, and we have for the subsequent events of starvation, simply,

$$\rho\left(\frac{dq}{dt}\right)^2 + \left[R_c + E_c + \frac{q}{\kappa}\right]\frac{dq}{dt} + A' = 0, \tag{56}$$

if the organism is to continue living in a state of starvation beyond the point represented by (54). For brevity take,

$$x = \frac{1}{\rho}\left[R_c + E_c + \frac{q}{\kappa}\right],$$

and

$$a^2 = 4A'/\rho.$$

Then a solution of (56) consistent with physical conditions is,

$$\rho\kappa \log_e\left[\frac{x}{a} + \sqrt{\frac{x^2}{a^2} - 1}\right] - \frac{\rho\kappa}{2}\left[\frac{x}{a} + \sqrt{\frac{x^2}{a^2} - 1}\right]^2 = \tau + C, \tag{57}$$

where C is the arbitrary constant of integration and τ, as before, the time.

Equations (56) and (57) should thus hold in practice for a period subsequent to the initial stages of starvation in cases where $\lambda\ddot{q}$ is not originally negligible, as well as from the very beginning of starvation when $\lambda\ddot{q}$ can be neglected at the start, as for example, in rats and pigeons, until the radical in (57) vanishes, that is, until

$$\begin{cases} \tau = -\dfrac{\rho\kappa}{2} + C, \\ \dot{q} = -\sqrt{A'/\rho}, \\ q = 2\rho\kappa\sqrt{A'/\rho} - (R_c + E_c)\kappa. \end{cases} \tag{58}$$

The value of τ as computed in the human case by the first of equations (58) is about 594 days following the onset of starvation. The range over which these equations may thus be expected to hold is far greater than the usual 30 to 40 day periods of fasting that can be observed in man, and unquestionably much longer than any period throughout which a human being or any other higher organism could tolerate complete abstinence from food.

Equations (51) to (58) have been applied (Wetzel*) to the case of complete starvation in man as represented by data on professional fasters as well as to data on fasting dogs, rats, guinea-pigs and pigeons. The results show that these equations are sufficiently general to represent the known trends for q, q^2, and $\dot{q}$. They constitute additional evidence in favor of the more general implications in equations (13), (27) and (47) by virtue of the fact that they are wholly in agreement with the particular condition $S_G = M' = 0$ which has its physiological counterpart in the experimental events of complete starvation.

Heat Production During Complete Starvation.—Further corroboration of the validity of the general equation (47) can be obtained by studying the theoretical trend of heat production, U, for example, under the foregoing conditions, namely, when $S_G = M' = 0$, and checking this against actual data on heat output in fasting subjects.

From earlier considerations we have, again, if U_s denote heat in calories per unit mass and time during complete starvation, to distinguish it from heat output U in equation (38) when $S_G \neq 0 \neq M'$,

$$U_s = \rho\left(\frac{dq}{dt}\right)^2 + E_c\left(-\frac{dq}{dt}\right) + A' \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{59}$$

for the simpler cases in which the harmonic term in (50) may be neglected. Now since $\dot{q} < 0$ whenever complete starvation is instituted in organisms that have once reached their own stationary state of growth, it is clear that, other things being the same, $U_s < U$ by the quantity $2E_c\dot{q}$. This condition cannot be tested in the human case because the positive value of $\dot{q}$ numerically equal to the negative value during fasting in adult man is reached soon after birth, that is, at a time when the harmonic term in (50) cannot be neglected.

The important point here, however, is that deliberate removal of the natural source of energy S will lead, theoretically, to a drop in heat production. This is precisely in accord with the widely known relationship between abstinence, or, conversely, administration of food, and basal heat output, the proper adjustment of which is carefully sought in all modern measurements of metabolism (Benedict, 1915; Benedict and Talbot, 1921; Du Bois, 1927; Krogh, 1916).

Heat production, moreover, will decrease as starvation continues and will become a minimum when $\dot{q} = -E_c/2\rho$. This condition is strikingly displayed in all observations on fasting organisms (A. V. Hill, 1911–12; Benedict, 1915; Horst, Mendel and Benedict, 1930; Phillips, Ashworth and Brody, 1932). It is especially well exhibited in data on man (Wetzel, 1932–33 *e*), because the continuous

* To be published.

negative increase in $\dot{q}$, theoretically to be expected according to (56), is so inconspicuous during the period of time allowed for such observations (about 30 days) that $\dot{q}$ remains sufficiently close to the critical value, $-E_c/2\rho$, a result, in turn, that will be assured if q itself remains close to the corresponding value,

$$q = \frac{\kappa}{2E_c}\left[4A'\rho - E_c(E_c+2R_c)\right]. \tag{60}$$

It is, consequently, of considerable interest to note that the greatest deviation from the value given by (60) does not exceed 2.69 per cent in the human case even at the end of a 30 to 40 day period of fasting.

The minimum value for U_s in (59) thus becomes

$$(U_s)_{\min} = \left[A' - \frac{E_c^2}{4\rho}\right], \tag{61}$$

that is, *less* than the normal maintenance heat output A' of healthy adult men who are not subjected to prolonged fasting. It is significant that this theoretical result is also in harmony with experimental observations (Wetzel, 1932–33 *e*). Some emphasis may therefore be put not only on the point that heat output U_s during complete starvation falls below the maintenance value A', but also on the fact that it tends, for the reasons just given, to a minimum, and hence to remain at a constant level below the maintenance value, A', in spite of the fact that body mass itself is continuously being lost, the total loss in mass, moreover, amounting at the close of observation to 22 per cent as compared with loss in q of about 6 per cent.

Partial Starvation.—Under normal circumstances of nutrition the source supplies energy in sufficient quantity as well as of the proper quality to meet the needs of growth and maintenance combined, or,

$$S = S_G\dot{q} + M', \qquad [\text{cal}\cdot\text{gm}^{-1}\cdot T^{-1}] \tag{62}$$

by rearranging symbols in equation (45). Thus, when the organism has energy for growth corresponding to $(S_G\dot{q})$, as well as energy for maintenance M', at its disposal, and can utilize this supply, the course of events will be that of ordinary growth and heat production as given by equations (33), (34) and (38). When $S_G = M' = 0$ we have $S = 0$, the case of complete starvation just previously discussed. But examples of partial starvation are obviously infinite in number and would be represented by independent changes in S_G and M'. These, however, could be classified theoretically into four main types: (*i*) administration of fuel for growth alone ($M' = 0$); (*ii*) for maintenance alone ($S_G = 0$); (*iii*) a fuel supply S_a qualitatively suitable for both growth and maintenance but quantitatively less than normal requirements ($S_a < S$); and lastly (*iv*) fuel qualitatively defective yet either quantitatively sufficient or, again, insufficient for growth and maintenance.

With remarkably few exceptions belonging to types (*ii*) and (*iii*) or to one of the several subvarieties in type (*iv*), there are as yet no experimental data* by

* See Robertson (1923), McCollum and Simmonds (1929), and Sherman and Smith (1922).

which the corresponding changes in the various quantities S, ρ, λ, κ, A', and E could be satisfactorily determined. Indeed, so far as the present results are concerned, existing data on defective nutrition afford only somewhat different material to which the integrals for q might be adjusted. But nothing is to be gained by such isolated procedures, for it is evident at this stage that among all possible trends for q, those consequent upon altered nutrition are likewise provided for in the general curve $q = \phi(t)$, and these, as we have seen, can be represented by the corresponding expressions for q. Equations (28), (34), (55), and (57), moreover, cannot rightly be construed to be interpolation formulae, and they should not, accordingly, be used in this sense. They should, in fact, only be used in conjunction with (38) or its equivalent for the primary purpose of evaluating the coefficients in (27); their application to data on growth alone is fruitless and cannot possibly get at the root of the matter.

What is needed and what comes much closer to satisfying the real objectives of this entire problem of growth, with its deep and intricate ramifications into the allied fields of nutrition and metabolism, are new experiments designed to provide the information by which the effects of undernutrition or overnutrition can be traced and measured in terms of corresponding changes which conditions such as these may be expected to produce in the fundamental dynamical quantities λ, ρ, κ, and P_φ.

To sum up the foregoing discussion on motion in systems completely or partially deprived of normal sources of energy, it may be said that experience with fasting subjects corroborates some of the main implications of equations (13) and (27). For the special character of the changes in body mass and in heat output subsequent to complete starvation are easily deduced from them and are accurately represented by the corresponding integrals. Some insight, moreover, has been gained into the connections between the actual physical circumstances of disturbed nutrition and the terms which appear in the explicit form of (13) as given by (47). But many other implications of these equations, as well as a closer study of the quantities they contain, must be left to future experimentation.

GENERAL SUMMARY AND CONCLUSIONS

The changes in heat production characteristically exhibited by growing organisms depend explicitly, as earlier papers in this series have briefly shown, on the rate of growth. This result, among others, has emerged from the concept that growth may be looked upon and treated as a mode of generalized motion. It has thus become the particular purpose of the present paper to develop the theoretical foundations as well as the chief consequences of this view.

The term "motion," as fully explained in the Introduction, refers to the whole set of phenomena associated with the *changes in size* which growing organisms undergo.

Aside from important distinctions recognized to exist between the biological processes of development as a whole and its subsidiary events, growth, differentiation, and organization, attention is first directed to the all important and

basic fact that growth depends intrinsically upon cellular self-multiplication. This leads to the rigorous definition of the quantity of growth q in terms of physical size z; the latter is expressed for many organisms simply in terms of body mass, since this is usually the most convenient measure of living substance.

A brief study of the purely graphical properties of a very general case of growth, $q=\phi(t)$, without reference to agencies that might possibly act to produce growth, introduces the more important kinematical aspects of the subject. What is called the motion of growth is represented in an interval of time by the nature as well as by the extent of the corresponding displacement of a point on this curve with respect to the coordinate axes q and t. The kinematical behavior of the system undergoing growth thus depends not only upon the position q but also upon the curvature at (q, t) and hence upon all of the quantities, q, $\dot{q}$, $\ddot{q}$, and t, at least.

More extended attention, however, has been directed toward giving a reasonably full exposition of the corresponding dynamical theory of growth. This implies a study of the agencies that initiate, maintain, and in general control the motion of growth.

Systems supporting growth manifest three chief properties which suggest that growth may be classed with other natural dynamical phenomena.

They possess, first, the property of growth inertia, which may be summed up in the statement that cellular reduplication, once initiated, will continue in its state of motion until acted upon to change that state. This property, by which the velocity of growth tends to persist under constant conditions, is discussed both for the case of growth in motion as well as for that of growth at rest.

Second, such systems liberate heat, but the significant feature of this from the dynamical point of view is that, with certain exceptions also considered, the production of heat per unit mass by a "growing organism" exceeds that of a similar organism familiarly described as "not growing." Of three parts which form the composite output of heat, and which together account for well-established trends of heat production in growing organisms, but two are motional and thus due to growth: the heat of dissipation and that of synthesis; the third component is nonmotional and is ascribable to pure maintenance of body tissues. The latter, accordingly, is solely responsible for the standard heat production of subjects who have reached the upper stationary state of growth.

Third, systems, the seat of growth, possess the important positional property, as opposed to the foregoing motional properties of inertia and dissipation, that the rate of growth depends, among other things, on the displacement of the system from its ultimate position of equilibrium.

In virtue of these three properties, it has been assumed that the Lagrangian equations of generalized motion, and in particular the associated equation of activity, when suitably modified, could be used for an analysis of growth. The three corresponding energy functions for the case of growth, T_m, V_m, and U, representing the kinetic energy of growth, the potential energy of growth, and the composite heat output per unit time and mass, which includes the dissipation function F_m, are formulated in terms of q or $\dot{q}$, as the case may be, since q

itself is chosen to represent the generalized coordinate of a system with one degree of freedom. This case is treated *in extenso*.

Associated with the functions T_m, V_m, and F_m are the three important constants, λ the inertia coefficient, κ the permittance, and ρ the resistance of growth, which help to determine the character of the resulting motion since they appear explicitly in the final solution for q and all of its derivatives.

Equally important, however, in fixing the motion are the quantities known as the generalized external applied force, P_g, and the applied power per unit mass for maintenance, M', with its corresponding heat reaction on the part of the system, A'. When $M' = A'$, as is usual for systems with natural sources of available energy, these quantities disappear from the equation of activity and take no direct part in determining the resulting motion. But if $M' \neq A'$, as for example in starvation, q becomes explicitly a function of $(M' - A')$ and the motion is deflected from its normal course by the heavy demands of maintenance A'.

A wide variety of existing experimental data on growth, heat production and energy exchange under natural conditions of nutrition, as well as similar measurements during complete fasting, are satisfactorily represented by the corresponding equations for q, U, and for other items of importance. These results, accordingly, are called upon to support the view that growth may be considered among the nonconservative dynamical phenomena in nature.

Data that might now be used to check the full implications of the present theory are wanting. Efforts in this direction, easily justified for their own sake, should have distinct practical worth. For, in the course of experiments designed to test the effect of various physical or physiological agents, such as vitamins, hormones, or radiations that are definitely known to influence growth, it should be possible, in view of the applications already made, to detect corresponding and even specific changes in the dynamical quantities ρ, λ, κ, and E, say, which play a fundamental role in determining the character of growth.

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RELATIVITY OF PHYSIOLOGIC TIME AND PHYSIOLOGIC WEIGHT*

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It is probable that nothing since the appearance of Darwin's *Origin of Species* has affected scientific and philosophic thought more than the introduction at the turn of the present century of the relativity theory, with its non-Euclidean space-time forms, and the electromagnetic theory of energy-matter with its quanta of wave-particles. Because of the complexity of living systems, biologists have not yet learned to make direct applications of the newer physics to biology. But the general outlook of biologists has been changed thereby. As an illustration we may cite the organismic hypothesis of biology, formulated by Claude Bernard and J. S. Haldane, which has taken on new life and prestige with the development of the field (or Whitehead's organismic) hypothesis of the physical world. The concept of space-time and relativity as it concerns growth has likewise come under discussion (Frank, '35). The purpose of the present paper is to indicate a *practical* application to growth in particular and to biology in general of the *idea* of relativity of time and weight.

I. RELATIVITY OF PHYSIOLOGIC TIME

The following familiar examples illustrate that *physiologic* time, as indicated by the tempo of changes in living organisms, is a relative concept and is not proportional to *chronologic* time, as measured by the movement of the hand of a clock adjusted to the rate of the earth's rotation around the sun.

1. A *chronologic* time unit, for example a day, has a different *physiologic* time significance in the life of different organisms, as, for example, mouse and elephant. If the normal life duration of the mouse is 2 years, and of the elephant 100 years, then in a certain sense one day in the life of the mouse has the same time-significance as fifty days in the life of the elephant.

2. A *chronologic* time interval has a different *physiologic* time significance at different ages. Thus, the 21-*day* incubation period of the chick has greater developmental significance—the organism goes through more epochal transformations during this time—than the 16-*year* period of postnatal life of the fowl.

3. A *chronologic* time unit has different *physiologic* time significance for different organs or tissues. Thus, while the circulatory, excretory, and nervous systems develop early and survive to the end of life, the reproductive system develops late and usually declines early. The literature on child development is full of such expressions as "mental age," "dental age," "anatomic age," "pubertal age," "developmental age," indicating a general recognition of the relativity of physiologic time.

* Paper 128 in the Herman Frasch Foundation Series, and paper 495 in the University of Missouri Agricultural Experiment Station Journal series.

4. Physiologic time may often be accelerated or retarded at will by food supply (2), temperature (3), hormonal action, (4), and other factors.

Since time has but relative significance in growth and development processes, it becomes important to have a practical method for comparing the relative equivalence, or correspondence, of physiologic time. The purpose of this section is to present such a method which is particularly applicable to the phase of growth and development following the major inflection.

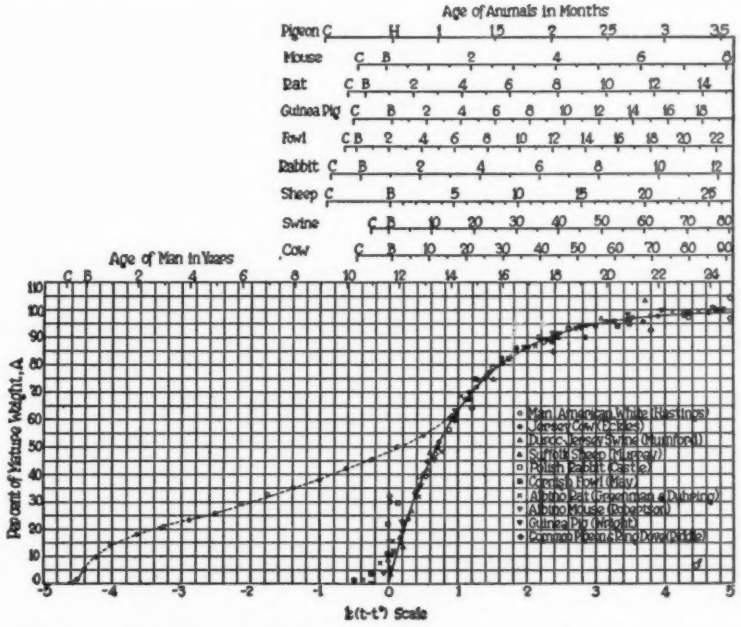

FIG. 1. Growth equivalence (during the phase of growth following puberty) between humans and animals plotted on a $k(t-t^*)$ grid (*cf.* p. 8, *Mo. Agr. Exp. Sta. Res. Bul.* 104).

The major inflection in the age curve of growth corresponds to puberty in higher animals, flowering in plants, and what is sometimes called "coming of age" in populations. It can be readily shown (5) that the time course of growth following the major inflection can be represented by the equation

$$\frac{W}{A} = 1 - e^{-k(t-t^*)} \tag{1}$$

in which W is the size (e.g., weight) of the organism (or population of organisms) at the age t; A is the size (value of W) at maturity (A is the asymtote of W); e is the base of natural logarithms; k is the relative, or fractional, decline in the velocity of growth with increasing age t; t^* is the position on the age axis where the extrapolated curve of equation (1) meets the age (t) axis; $(t-t^*)$ is, thus, age

as counted from point t^*; W/A, the fraction of the mature weight at age t, is thus a function of the product of the velocity constant of growth, k, and age as counted from t^*.

The k in equation (1) represents the rate of approach to the mature size, A, during growth. Thus we found (6) that k of a cow is 0.054; of a rat, 0.644. Therefore the rat approaches maturity $1 \times 0.644/0.054 = 11.9$ times as rapidly as the cow; or 1 month in the rate is equivalent to $1 \times 0.644/0.054 = 11.9$ months in the cow; or 1 month in the cow is equivalent to $1 \times 0.054/0.644 = 0.08$ months in the rat. We thus have a *practical* method for evaluating the relativity of time in different organisms.

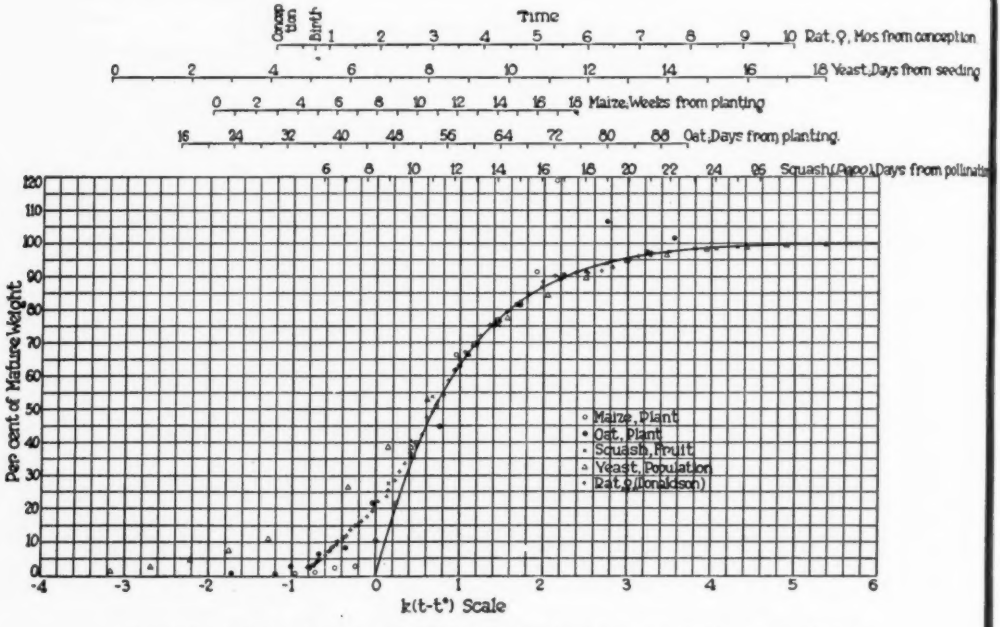

FIG. 2. Equivalence of age for animals (rat) plants (maize, oats, squash) and populations (yeast) (*cf.* p. 46, *Mo. Agr. Exp. Sta. Res. Bul.* 102).

Let us illustrate this idea graphically by estimating the age in pigeons, mice, rats, guinea pigs, rabbits, sheep, swine, and cattle corresponding to age 15 years in humans. It is evident from equation (1) that for a given value of $k(t-t^*)$, there is one, and only one, value of W/A. If, therefore, the values of W/A of two or more species are plotted against the corresponding values of $k(t-t^*)$, the resulting curves will necessarily coincide. After the W/A data are plotted on the $k(t-t^*)$ grid, the absolute age-scales are laid off, as shown in figure 1, and the ages of the different species corresponding to 15 years in humans are easily read from the chart. Incidentally, figure 1 shows that the pre-pubertal phase of

growth in humans (preceding the age of fourteen) is *extraordinarily* long as compared to all others, pigeons, mice, rats, guinea pigs, rabbits, sheep, swine, and cattle. The extraordinary length of the juvenile period in humans should be of particular interest to educators, psychologists, and sociologists.

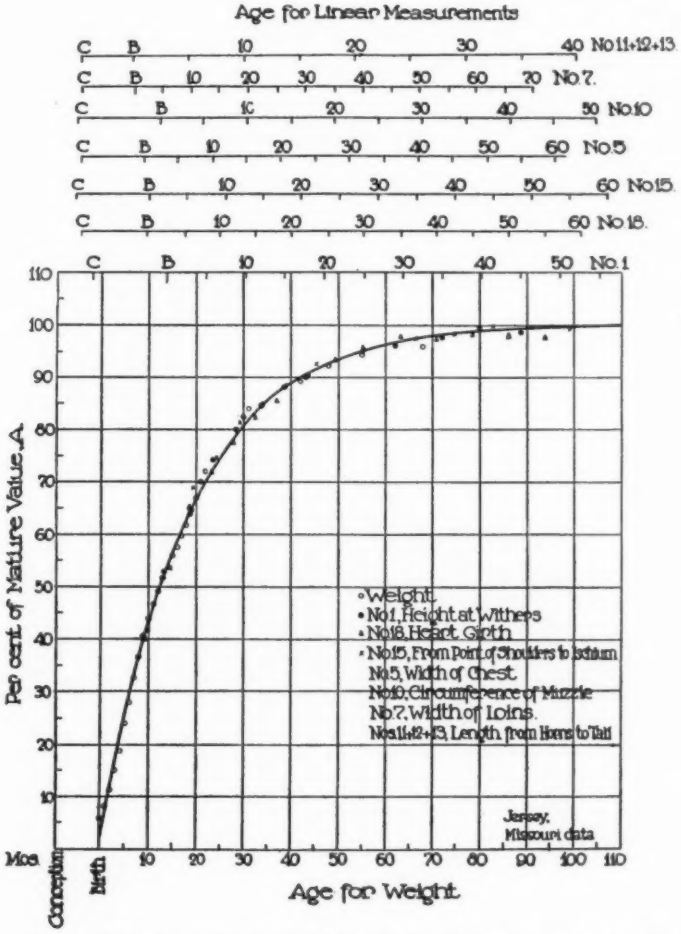
Age for Linear Measurements
C B 10 20 30 40 No 11+12+13
C B 10 20 30 40 50 60 70 No 7.
C B 10 20 30 40 50 No 10
C B 10 20 30 40 50 60 No 5
C B 10 20 30 40 50 60 No 15.
C B 10 20 30 40 50 60 No 18.
C B 10 20 30 40 50 No 1
Per cent of Mature Value A
110 100 90 80 70 60 50 40 30 20 10
Mos
Conception
Birth
10 20 30 40 50 60 70 80 90 100 110
Age for Weight
• Weight.
• No 1, Height at Withers
• No 18, Heart Girth
• No 15, From Point of Shoulders to Ischium
No 5, Width of Chest.
No 10, Circumference of Muzzle
No 7, Width of Loins.
No 11+12+13, Length from Horns to Tail
Jersey, Missouri data

FIG. 3. Equivalence of age for weight growth and linear growth of cattle (*cf.* p. 12, *Mo. Agr. Exp. Sta. Res. Bul.* 103).

Similar age-relativity charts have been prepared for growths of animals, plants and populations, figure 2 (7); weight growth and linear growth, figure 3 (8); and for relativity of senescence, Fig. 4 (9).

II. RELATIVITY OF PHYSIOLOGIC WEIGHT

The following familiar examples illustrate that just as a chronologic time unit, such as a day, has different physiologic significance in the life of different animals, so a gravitational weight unit, such as a pound, has different physiologic significance in the life of different animals.

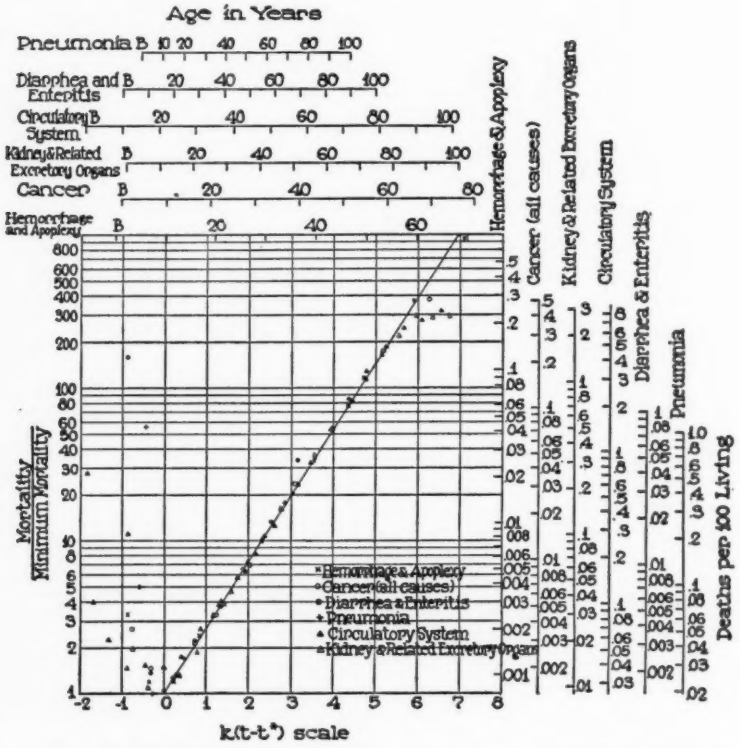

FIG. 4. Senescence equivalence between various organ-systems as measured by specific mortality due to the breakdown of corresponding systems (*cf.* p. 31, *Mo. Agr. Exp. Sta. Res. Bul.* 105).

1. Large animals are less active *per unit live weight* than small. This may be substantiated by general observation and also from experiments on horses (10).

2. The endogenous metabolism of energy, nitrogen, and sulphur *per unit live weight* of animal decreases with increasing live weight (11), indicating that physiologic weight is not identical with gravitational weight.

3. The productivity of milk, eggs, meat, wool, and muscular work *per unit live weight* of animal likewise decreases with increasing live weight of animal (12).

4. The physiologic significance *per unit live weight* may often be increased or

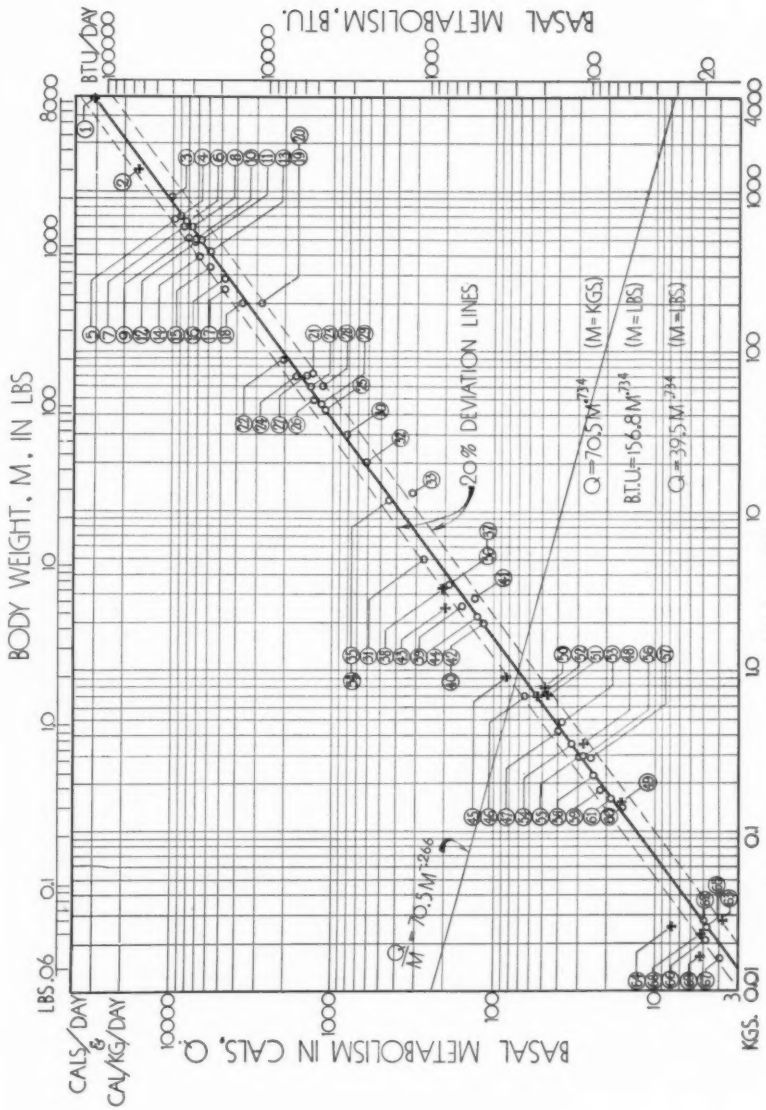

FIG. 5. Basal energy metabolism, Q, plotted against body weight, M, on a logarithmic grid (*cf.* p. 12, *Mo. Agr. Exp. Sta. Res. Bul.* 220). The numbers enclosed in circles refer to the position of the corresponding values recorded in Table 1 (appendix) of Missouri Agr. Exp. Sta. Bul. 220. Data points represented by crosses were not included in fitting the given equations on the charts to the data. The heavy continuous line represents the equation on the chart in which Q is kilocalories of energy for body weight M.

decreased at will by regulating food supply, activity, hormonal action and other factors. It is generally known that the activity, and the "active mass," is greater per unit of live weight in thin than fat animals.

Since *gravitational* live weight has but relative significance, it becomes important to have a practical method for comparing relativity equivalence, or correspondence, of *physiologic* weight. The purpose of this section is to present such a method for warm-blooded animals.

An extensive investigation (13) on the energy metabolism of warm-blooded animals ranging in live weight from 3850-kg. (8500 pound) elephant to 16-gm. (0.035 pound) mice indicates that basal energy metabolism does not increase linearly with body weight, but with the 0.73 power of body weight, as shown in Fig. 5. Likewise, endogenous nitrogen and sulphur excretion vary with the 0.73 power of body weight. It is reasonable to conclude from this fact that the nutrients required for maintenance under normal (rather than "basal") conditions likewise increase not with simple body weight, but with the 0.73 power of body weight. Moreover, it appears probable from available data and from theoretical considerations that the productivity of animals [production of milk, eggs, meat (growth), muscular work] varies with a fractional power (of the order of 0.73) of body weight.

If the aforecited facts and reasonings are correct, then the physiologic unit of mass should be not simple gravitational weight, but a fractional power of weight, as indicated by the equation

$$\text{Physiologic mass} = AW^n \tag{2}$$

in which W is live weight (i.e., gravitational weight), n a fractional power of the order of 0.73, and A a parameter the value of which is dependent on the unit employed. (Thus in Fig. 2, the value of A is 70.5 when live weight is in kgs. and energy in kilocalories; 156.8 when live weight is in pounds and energy in B. T. U's.; 39.5 when weight is in pounds and energy in kilocalories. The value of the exponent n, on the other hand, remains 0.73 in all cases.)

Theoretically, equation (2) indicates that the "active mass" or "physiologic mass" of mature animals of different species is gravitational live weight raised to, roughly, the 0.73 power. We have shown (14) that the visceral organs, as well as cross-section areas of vessels and surface area of the body, tend to vary with from $\frac{2}{3}$ to $\frac{3}{4}$ power of body weight. There is, thus, a morphologic basis for the variation of the metabolic, and consequently productive, processes of animals. There is no doubt a physico-chemical equilibrium between the various functional—including metabolic and productive activities—and morphological aspects of the animal which will some day be worked out in some such manner as Henderson ('28) worked out the physico-chemical relation between the various blood components. For the present, the suggestion is made that the metabolic and productive processes of animals vary with the 0.73 power of live weight because the "active" visceral organs (contrasted to the connective and supporting tissues) vary with the 0.73 power of body weight. Cross section areas and surface areas of the channels which connect the cells from the vis-

ceral organs with the internal and external environments must necessarily vary with the $\frac{2}{3}$ to $\frac{3}{4}$ power of total live weight. This more or less empirical reasoning leads to the suggestion that the 0.73 power of gravitational weight is a more suitable unit of *physiologic* weight than is simple *gravitational* weight.

SUMMARY

A given *chronologic* time unit has a different *physiologic* time significance in different organisms, and in the same organism at different ages.

For investigations of comparative growth or senescence, it is suggested that $k(t-t^*)$ be used as unit of physiologic time. Age curves of growth or senescence of different species (pigeons, mice, rats, guinea pigs, rabbits, sheep, swine, cattle, humans) coincide when thus plotted against $k(t-t^*)$, and correspondence of physiologic age is indicated.

It is suggested in the same spirit that for comparative purposes the 0.73 power of live weight be used as "physiologic weight" unit instead of simple *gravitational* weight.

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THE ROLE OF l-ASPARTIC ACID IN DEVELOPMENTAL GROWTH

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This is a report of the evaluation of l-aspartic acid in terms of the developmental growth of Obelia geniculata. There is evidence presented which indicates this amino acid has a specific stimulating effect on that phase of growth in which differentiation is the most obvious activity.

INTRODUCTION

Work hitherto reported allows no decision on the possibility that l-aspartic acid, as a presumed constituent of living tissue of general distribution, is a determining or specific factor in growth. Although Holt ('28) reports the production of giant yeast cells is markedly stimulated thereby, and Koser ('16), Sjollema and Zander ('23), Gordon and M'Leod ('26), and Sahyun et al. ('36) that bacterial growth is more luxuriant in its presence, these observations only suggest the compound as a good source of carbon and nitrogen. But l-aspartic is apparently an integral component of living matter. It therefore may be that it is something other than a building stone, a component of the reaction basis of living, or a source of energy. Indeed, like other compounds of similar situation so far studied (Hammett, '35, '36a.b), it may be as pointed out in *The Nature of Growth* ('36) a specific determining participant in some growth process essential for the bringing of the organism to complete the functioning maturity. The matter has been put to proof.

MATERIAL AND METHOD

As usual the colonial-living form of the marine hydroid *Obelia geniculata* was the test animal. This organism is suitable for exploration of this kind since in it the several basic developmental and metabolic activities can be studied separately and expressed by numerically recordable changes. Although detailed description of the animal and its growth has been given (Hammett, '33, '35a.b, '36d) brief recapitulation is indicated.

1. *Initiation.*—The animal first shows as a small swelling on stalk or pedicel. Certain processes must have taken place in the ground substance from which this swelling comes before it begins. These are the developmental processes of growth initiation. Five types of hydranth initiation may be distinguished. There is (1) initiation by anlagen formation where no hydranth has previously existed. There is (2) initiation of new hydranths by recurrence from pedicels on which functioning hydranths, or (3) senile hydranths, or (4) empty hydrothecae were present at the beginning of observation. There is initiation (5) by regeneration from broken pedicels. And there is initiation (6) by anlagen for-

mation of new gonophores. Finally there is initiation (7) of stolon growth from the cut end of the hydrocaulus which is possibly akin to vasculogenesis. Thus in an obelia colony seven separate expressions of one developmental activity may be had under the heading Initiation.

2. *Proliferation.*—The bud, growing out on its pedicel, enlarges and expands into an inverted cone. Although this phase is factored by differentiation since several cell types are present, and by organization since the structure has form; yet it can be assumed that the major growth factor is proliferation since the growth is largely one of simple expansion and extension, an expression of increase in cell number. Eight types of proliferation expression may be distinguished. There is (1–6) proliferation of the six structures derived from initiation exclusive of the stolon. Measurement of growth in length of this structure is not made routinely. There is proliferation of (7) hydranth and (8) gonophore buds already present at beginning of observation. It is the undifferentiated growth from these eight separate sources in an obelia colony which is grouped under the heading of Proliferation.

3. *Differentiation.*—The next stage of hydranth development is the accumulation of the internal cellular mass as a truncated peduncular cylinder at the distal end of the hydrotheca which is beginning to form as a separate entity. The change is one of cellular and structural specialization. Although proliferation may play a part since there is enlargement, and although organization contributes its share since there is new segregation, it is assumed that the major factor in the new development is differentiation since specialization is evident and since this does not go on to functional segregation. Ten expressions of differentiation are distinguished. There is (1–6) that from each of the six sources of hydranth inverted cone production, and that from (7) hydranths already present as cones. There is differentiation of already present immature (8) gonophores and of (9) gonophores derived from originally present buds. And finally there is (10) stolon metaplasia. It is the specialization growth from these ten separate sources in an obelia colony which is grouped under the heading of Differentiation.

4. *Organization.*—The final *growth* change is the formation of tentacles, mouth and gastrovascular cavity from the cell mass of the pedunculated cylinder, and the sequestration of the completed animal within its hydrotheca as a functioning entity. Although other developmental activities may participate, organization is the chief factor concerned in the process since it is this change which produces that cellular segregation essential to the formation of a functionally and structurally coordinated unit. With the exception of structures derived from complete feeding hydranths present at the beginning of observation, all the several derivatives of differentiation are potential sources of organization. Dropped is that of metaplasic stolons. Added is that of hydranths which are at the differentiation stage at beginning of observation. Thus, under the heading of Organization there is in each obelia colony a potential total of nine separate expressions of this developmental activity.

5. *Maintenance and Regression.*—Sooner or later, because of intrinsic devel-

opmental or extrinsic environmental conditions, the complete animal ceases its feeding and other activity and shrinks into the hydrotheca. The function of the complete animal is that of ingestion and preparation of materials for the growth and energy requirements of the colony as a whole. This is called maintenance metabolism. The percentage of animals which stay at the feeding stage during the course of experiment is the index of maintenance reaction to experimental conditions. The percentage which ceases functioning and goes on to the next or senile stage is an index of what is called physiological regression.

6. *Catabolism.*—Once the animal has become senile and is no longer functioning it undergoes disintegration and its substance is carried away by the downstreaming current of its pedicular hydroplasm. This dissolution which occurs from within the function of which is to make way for a new organism by recurrent growth, is an expression of catabolic activity. The percentage of organisms which undergo this change is the index of catabolism.

Briefly, and openly, an obelia colony is potentially capable of expressing growth change from 34 different kinds of observable sources and of metabolic activity from two. It is the differential reactions of these singly and grouped according to developmental expression, by experiment and by concentration, which determines whether and wherein a given amino acid or other naturally occurring component of living matter of general distribution is significant to growth.

The methods of collecting, culture, and general laboratory procedure have been described elsewhere (Hammett, '33, '35a.b). About 500 animals are used for each experiment, equally divided between test and control cultures. These are run simultaneously under like conditions of temperature, illumination, and pH. All solutions are made with fresh sea water collected in white enamelled buckets. Culture media similarly. Four changes into fresh sea water are made during the 24 hour course of experiment. The l-aspartic acid used here was purified by Dr. Theo. Lavine to constant titration and rotation values. Stock solutions containing 0.067 gram l-aspartic acid in 100 cc. fresh sea water provided daily the aliquots from which the culture solutions of desired concentration were made. Stock solutions were brought to the pH of the solvent by appropriate amounts of N/10 NaOH.

Fifty-eight experiments were run at six different l-aspartic acid concentrations with close to 29,000 animals and 1400 gonophores.

The methods of arriving at estimate of reaction are simple. First calculated is the percentage extent to which *each* change described above is expressed in the single experiment. Test direction of difference from control is recorded for each. The consistency of this deviation among the several experiments done at the given concentration is then recorded. This shows whether test reaction of the single change tended to be greater, less, or equal to that of the control. These are the consistency by experiment data. Next the raw data of the several experiments done at a given concentration are combined and the percentage expression of change for each potentially therefor is calculated. The direction of test difference from control in these values is also recorded as a greater, lesser,

or equal progression. Thus two indices are had of test reaction for each potentiality; the consistency by experiment and the reaction in terms of total number of animals available therefor at a given concentration. Because of uncontrollable factors either index by itself may in some cases be unreliable. Decision as to reaction is therefore derived by combining the two indices. The result is recorded in terms of plus, minus, and no change for each potentiality. Such a record is found in table 1 of the uracil report (Hammett, '36d). From it demon-

TABLE 1

TREND OF TEST DEVIATION FROM CONTROL WITH RESPECT TO DEVELOPMENTAL AND METABOLIC ACTIVITY IN l-ASPARTIC ACID CULTURES

Also the Number of Experiments, Colonies, Hydranths, and Gonophores at the Stated Concentrations

M/1000×	200		100		50		25		12.5		6.25	
No. Expts.	8		12		12		8		8		10	
	Cont	Test	Cont	Test	Cont	Test	Cont	Test	Cont	Test	Cont	Test
No. Colonies	120	120	180	180	180	180	120	120	120	120	136	136
No. Hydranths	2090	2108	3062	3055	3098	3107	2045	2053	2093	2081	2321	2331
No. Gonophores	71	57	169	172	137	156	119	107	125	137	99	94
GROWTH	+ − =		+ − =		+ − =		+ − =		+ − =		+ − =	
Initiation	3 2 2		1 2 4		3 3 1		3 3 1		1 2 4		0 2 5	
Proliferation	2 3 4		1 1 6		4 1 3		2 5 1		0 4 4		2 2 4	
Differentiation	1 2 5		3 1 4		4 1 3		2 2 5		3 2 3		5 3 1	
Organization	1 2 3		0 0 7		1 2 4		3 0 4		0 2 6		0 2 6	
METABOLISM by single experiment												
Maintenance	2 3 3		6 4 2		4 6 2		3 5 0		2 2 4		1 8 1	
Catabolism	3 5 0		6 6 0		4 6 2		4 3 1		4 3 1		3 6 1	
METABOLISM by combined experiments												
	Cont	Test	Cont	Test	Cont	Test	Cont	Test	Cont	Test	Cont	Test
Regression	16.1	16.4	14.7	13.9	18.7	18.5	15.6	16.7	21.9	23.1	16.7	20.3
Maintenance	83.9	83.6	85.3	86.1	81.3	81.5	84.4	83.3	78.1	76.9	83.3	79.7
Catabolism	70.0	72.8	63.7	65.4	68.8	67.0	64.4	65.1	79.6	82.7	64.9	62.2
	Increase in % Regression due to l-Aspartic Acid Cultures											
1935	1.8		−5.4		−1.1		7.1		5.5		21.6	
1933	—		—		—		7.4		18.5		36.0	

stration may be had of particulate reaction within a developmental clone. For example in the cited case, new hydranth production by recurrence was stimulated in the presence of uracil while other expressions of initiation were not so affected. This allows assumption that it was not the developmental activity of initiation *per se* but that of recurrence which was favored. It is not necessary to give such a table for l-aspartic acid since evidence of particulate reaction is unsure. Instead there is given a tabulation of reaction grouped according to developmental activity. That is to say, the table gives—on the basis of the

classification of the preceding paragraphs—the number of times test expression of opportunity for any given developmental or metabolic activity was greater, less, or equal to that of control. For example, the table shows that test reaction was greater than control in three, less in two, and equal in two of the seven types of opportunity for expression of the developmental activity of initiation at M/200,000 l-aspartic acid. The table does not tell which of the several opportunities for initiation was expressed to greater, less, or equal degree. It is to be remembered that these condensed consistency data are derivatives of the consistency by experiment and reaction by totals data and are therefore valid indices of reaction trend.

Analysis of the data in table 1 will be given in some detail as a demonstration of the procedure used in coming to decision.

RESULTS

A definite and distinct trend to enhancement of differentiation expression was the outstanding reaction to l-aspartic acid.

The evidence is as follows.

A. *Taking the data as a whole.* Test progression from the relatively undifferentiated cone to the definitely specialized pedunculated cylinder stage tended to be greater than control in four of the six sets of experiments. It was less in none. Test differentiation was greater in 18, less in 11, and equal in 21 of the 50 expressions presented by the six sets of experiments. When each type of potentiality for differentiation is combined into one value for the six sets of experiments test progression is seen to have been greater in four and less in but one of the ten opportunities.

No such response obtained in the other growth brackets.

Test initiation expression was greater than control in none of the six sets of experiments. It was less in one and equal in five. Test proliferation and test organization expression were both greater than control in but one of the six sets of experiments while they were less in two and equal in three.

Further, test initiation was greater than control in 11, less in 14, and equal in 19 of the 42 expressions presented in the six sets of experiments. Test proliferation was greater in 11, less in 16, and equal in 22 of its 49 expressions; and test organization was greater in but five, less in eight, and equal in 30.

Thus regardless of low ineffective M/200,000 concentration and toxic high M/12,500 and over concentrations the differentiation response was definite in trend and distinct from that of the other growth expressions.

Overt toxic reaction was first shown at M/12,500. The evidence is the definite trend to general growth retardation present in three of the four developmental brackets, differentiation being the exception. Moreover when the four developmental activities are combined, test growth is seen to have been less than control in ten and greater in but four of its 31 expressions. Excluding differentiation as enhanced consistently, the combined data for initiation, proliferation, and organization show lesser test growth in eight and greater in but one of the remaining expressions.

The table shows no such retardation in any of the lower concentrations. Indeed in the immediately preceding one of M/25,000 test growth was greater in one, less in one, and equal in two of the four brackets; while in the combined data it was greater in ten, less in ten and equal in 11 of its 31 expressions. The relation between greater and lesser growth remains the same even with removal of the differentiation data. Further evidence that this is the beginning of toxicity is the fact that regression is sharply increased at M/6250 and the fact that catabolism tends to slow down; two reactions which are consistent with and usually accompaniments of harmful effect.

B. It is legitimate to analyse *the results exclusive of the toxic range.* In so doing it is seen that test differentiation expression was greater than control in two of the four sets of experiments and less in none: that test initiation was equal in all; that test proliferation was less in one, greater in one, and equal in two; and that test organization was greater in but one and equal in three.

Further, test differentiation was greater in ten, less in but six, and equal in 24 of the 40 expressions presented by the four sets of experiments; while, test initiation was greater in ten, less in ten, and equal in eight of its 28 expressions; test proliferation was greater in nine, less in ten, and equal in 13 of its 32 expressions; and test organization was greater in five, less in four, and equal in 27 of its expressions.

Finally test differentiation was greater than control in five and less in but one of the ten potentiality types when each is combined into a single value for the four experiments; while test initiation expression was greater in but two, less in three, and equal in two of its seven potentiality types; and test proliferation was greater in three, and less in three of its eight types; with organization greater in one and less in two of its seven responses.

The definiteness and distinctness of the differentiation reaction is maintained.

It has been stated that l-aspartic acid in M/200,00 concentration was without influence. The evidence is the fact that test progression was here quite the same as control in each of the four developmental brackets, and the fact that this equilibrium was maintained when the data are combined, for test growth was greater in seven, less in nine, and equal in 14 of its 30 expressions. Further, regression was essentially the same in test and control, both by experiment and by percentage of totals.

C. It is legitimate therefore to analyze *the results exclusive of those in the non-effective and toxic ranges;* viz. from M/100,000, through M/50,000, to and including M/25,000.

First it is here seen that where test differentiation was greater than control in two of the three sets of experiments and less in none, test initiation was equal in all, test proliferation was greater in one, less in one, and equal in one, and test organization was greater in one and equal in two.

Next it is found that test differentiation was greater than control in nine, less in but four, and equal in 12 of the 25 expressions presented by the three sets of experiments; that test initiation was greater in seven, less in eight, and equal in six of its 21 expressions; that test proliferation was greater in seven,

less in seven and equal in ten of its 24 expressions; and that test organization was greater in four, less in but two, and equal in 15 of its 21.

Finally, test differentiation was greater in five, less in but one, and equal in three of its ten potentialities when each type is combined into one value for the three sets of experiments. On the other hand, test initiation was greater in two, less in two, and equal in three of its seven potentiality types; test proliferation was greater in three, less in three, and equal in two of its eight types; and test organization was greater in two, less in one, and equal in four of the seven given expressions.

Again definitely and distinctively is differentiation shown to be enhanced in the presence of l-aspartic acid, as contrasted with the essential lack of reaction of the other developmental potentialities. This specific reaction also obtained in preliminary work done in 1933, the results of which though not given here are available to the interested.

Note is here made of the fact that a little trend to an enhanced organization is present in the data uncomplicated by non-effectiveness or toxicity, and the fact not shown by the table that growth from broken pedicels from initiation up through differentiation of the regenerated hydranths tended to be fairly consistently better in tests than in controls. This will be expanded upon in the discussion.

The data give no evidence that metabolic activity as expressed in maintenance and regression of the feeding hydranths, and catabolism as shown by disintegration of the senile animals, was essentially affected by l-aspartic acid in concentrations below M/6250. Though some hint of increased regression beginning at M/25,000 is had both in the 1933 and the 1936 data, this was insufficiently consistent to justify conclusion of reaction. The same can be written of the response at M/12,500. It was only at the toxic M/6250 concentration that maintenance and catabolism were consistently and deeply cut and regression increased.

DISCUSSION

Summarizing

Differentiation in Obelia is enhanced by l-aspartic acid.

The evidence is secure. The reaction is exhibited both in these and in the unpublished but available 1933 experiments. The identity in trend in the two series done in two different seasons with two different sets of workers is sustaining. That it persists despite toxic retardation of other growth expressions in M/12,500 and M/6250 is supportive. That expression of no other developmental activity was affected in either direction to significant degree or consistently demonstrates the essential specificity of the differentiation reaction. The fact that other developmental activities were stable in the presence of the amino acid indicates the reaction of differentiation was *sui generis* and independent.

The matter of the trend towards enhancement of new hydranth production and growth continuance from broken pedicels deserves analysis. This growth is regeneration and its initiation is based in a reconstitution (Hammett, '36a.c,

Child, '31). This reconstitution is not simply an expression of cyto-, histo-, and morphogenesis. It is more fundamentally an expression of a chemical reconstitution of the cytoplasm of the cells which go on to re-constitute the new animal. Of the cells which if the accident of a broken pedicel had not occurred would have continued their structural and functional status as pedicular constituents with the cytoplasmic constitution pertinent thereto.

Now this chemical reconstitution of the cytoplasm of the pedicular cells is of the nature of a setting of the cells to that chemical specialization which leads to new animal production. It is such chemical specialization which is the basis of differentiation (Hammett, '36c). Therefore, since l-aspartic acid is definitely a stimulus to differentiation expression, it may be that the trend to enhanced regeneration is the to-be-expected response of its basic specialization process. If this interpretation be correct, the data are consistent with the finding that l-aspartic is a stimulus to differentiation and they may also be taken as experimental evidence supportive of the *a priori* concept that there is an element of differentiation in the chemical reconstitution processes of regeneration initiation.

An alternative is possible. Glycine is a specific stimulus to regeneration in Obelia (Hammett, '36a). It could be that this amino acid is split from l-aspartic in metabolism. The potentiality is shown in the formula; $COOH(NH_2)CH\text{-}CH_2COOH$. If glycine is so produced it might be a factor in the trend to enhanced regeneration observed in these experiments. Both glycine and l-aspartic acid may be concerned. The data are provocative. As they stand they suggest experimental demonstration has been given of the presence of at least two separate processes concerned in the initiation of regeneration. One in which glycine is a specific participant, and one in which l-aspartic acid is significant. More than one process is of course to be expected. Although the point of participation of glycine is unknown, it may be assumed from these experiments that that of l-aspartic acid is identifiable with some process productive of cytoplasmic chemical specialization.

Noted was the slight trend towards better than usual expression of organization in the effective non-toxic concentration range. This may not be attributed to an increased regression (Hammett, '36b) of the complete hydranths. It was insufficient in degree and general occurrence to be taken as a reaction *sui generis*. It therefore can be assumed to be a natural reaction to stimulation of an antecedent or the differentiation phase of developmental growth (Hammett and Hammett, '32). The fact and the nature of its occurrence is consistent with the conclusion that l-aspartic acid is stimulative of differentiation expression in Obelia.

Of final consistence is the fact that d-glutamic acid is also a stimulus of differentiation in obelia. For both d-glutamic acid and l-aspartic are the only known naturally occurring dicarboxylic amino acids of general distribution, and the only known structural and compositional difference between the two is that d-glutamic acid has one more CH_2 group in its chain than l-aspartic has.

There is little if any evidence that l-aspartic acid has a specific dynamic effect on the feeding animals. Maintenance and regression were essentially unaffected until the toxic M/12,500 concentration. It is barely possible that the slight relative increase in percentage regression of the tests at the essentially non-toxic concentration of M/25,000 is expression thereof (Hammett, '36a). But decision is hardy. This is consistent with the conflict in the literature where metabolic stimulation by l-aspartic acid is found in some places (Rapport and Beard, '28, Burge, '18) and not in others (Atkinson and Lusk, '18, Burge et al, '27, Ort and Bollman, '27). The paucity of regression stimulation in non-toxic concentrations is in marked contrast to the effect produced by d-glutamic acid (Hammett, '36b). Here regression was not only marked, it was definite even at the low M/400,000 concentration.

Without drawing conclusion attention is called to the fact that this increase in regression stimulus occurs when an additional CH_2 group is introduced into the chain and the fact that a like reaction under like circumstances occurs in the case of glycine and alanine (Hammett, '36e). Here also regression in the presence of alanine of one more CH_2 group was greater than in the presence of glycine of one less, and here also the only known structural and compositional difference between the two amino acids is this additional CH_2 group.

While it is possible the coincidence is fortuitous and without significance there is implication of a correlation between chemical constitution and metabolic influence which should not be neglected, and there is indication that something other than the nitrogenous group is responsible for the specific dynamic effect of amino acids. This is in accord with the postulate of Benedict ('12).

As far as toxicity is concerned such has been found for aspartic acid in other types of experiments as would be expected (King, '12, Newburgh and Marsh, '25).

SUMMARY AND CONCLUSION

Fifty-eight experiments with close to 30,000 Obelia hydranths half of which were exposed to l-aspartic acid in six different concentrations show that in the non-toxic effective range the amino acid is a specific participant in some process concerned with differentiation expression; that it has no apparent effect on any other developmental activity; and that regression, maintenance, and catabolism are essentially unaffected thereby.

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EXPERIMENTAL FINDINGS CONCERNING THE ELECTRO-DYNAMIC THEORY OF LIFE AND AN ANALYSIS OF THEIR PHYSICAL MEANING

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APPRAISAL: NORTHROP AND BURR

Appraisal in terms of contemporary science is a first step in integration. Integration is the solid foundation of progress. Pre-publication editorial appraisal is not usual. An attempt will, however, be made by GROWTH to assist integration through appraisal when such is assented to by authors. This will be no valuation. Simply a sketch of possible relations.

This paper of Northrop and Burr gives a new angle of vision to the problem of growth: based as it is on the broad concept that "living systems are complex electro-dynamic fields" which at one and the same time determine and are determined by that constellation of chemical atoms, molecules, groups, ions and reactions which is a living thing.

It indicates that the electro-dynamic field is unique and specific to the system as is the chemical constitution and reactions. It gives experimental demonstration that changes in activity of the system are detectable as changes in electro-dynamic field. And it extends these records to conditions of ovulation and cancer wherein growth activity is a participant.

What is important is that this work of Burr and Northrop opens up possibility of evaluation of the nature of participation and coordination of the electro-dynamic field in the chemical activities of growth and development. This in turn may lead to precise and meaningful mathematical statement of the course of growth.—F. S. HAMMETT.

The crucial difficulty in any discussion of the relation between biology and physics is the problem of organization. It may be taken as definitely established by the body of physiological chemists since Lavoisier that living creatures possess physico-chemical constituents, but it has not been so certain that the organization of these constituents could be understood in physico-chemical terms. In fact, an accumulation of data and reflections brought forward by Driesch, J. S. Haldane, Child, Spemann and Köhler among others has convinced a considerable body of scientists that biological theory requires the supplementation of the concepts of inorganic science with purely biological terms. Thus, such notions as "entelechy," "life," "organizer," "physiological gradient" and "Gestalt" have been introduced.

It cannot be denied that these concepts have been very suggestive in directing attention to certain qualitative characteristics of living organisms. Nevertheless, all such concepts have suffered from two fatal weaknesses: (1) With but few exceptions they are elusive and difficult to determine and to apply

experimentally and quantitatively, and (2) even when applicable, the relationship of these biological concepts to physical and chemical concepts has been difficult to formulate in any meaningful way. Thus, instead of illuminating the relationship between the physico-chemical constituents and the organization of those constituents in living things, the introduction of these qualitative and purely biological concepts merely deepened the gulf between the two. In other words, the vitalistic, teleological, organic, biologic and holistic theories reemphasized the increasing acuteness of the problem of organization but made no fundamental scientific or philosophical contribution towards its resolution.

The reason for this failure is not difficult to discover. If any of the above theories be formulated systematically there results an intuitively and qualitatively conceived philosophy of science of the Aristotelian type with irreducible formal and final causes. If the same is done with the physico-chemical constituents of biological processes there results a quantitatively and atomistically conceived philosophy of science of the Democritean type which is mechanistic and denies the existence of irreducible formal causes. The attempt to solve the problem of organization by supplementing the atomic concepts of the traditional chemistry of living creatures with the qualitative organic concepts suggested by their perceived organization failed because it was a contradiction in terms. The Aristotelian and Democritean philosophies of science do not combine (Northrop, '31a).

What, then, are we to do? The organization of living matter seems to involve more than the atomic and kinetic concepts of traditional physico-chemical theory can provide, yet the attempt to supplement the physico-chemical concepts with biological concepts has been inexact and infertile scientifically and self-contradictory philosophically. Clearly, a different mode of attack is required. Moreover, the character of this new approach is indicated. Since the attempt to relate the organization of living creatures to their physico-chemical constituents by an appeal to extra-physico-chemical categories has failed, there seems to be no alternative but to look for a solution of the biological problem of organization in terms of a revised theory of the physics and chemistry of life. Perhaps it is a faulty conception of the physico-chemical rather than the utter inadequacy of any physico-chemical theory whatever, that is at the heart of the difficulty.

It was considerations such as these which caused Northrop in 1921, after considerable analysis of the biological materials, to turn to an examination of the new concepts necessitated by the new physics for a key to the resolution of the biological problem of organization. He became convinced that the difficulty could be met only by a philosophy of science which provided meaning for irreducible field and organic factors within an atomistic theory of science of the Democritean type. In 1923, by means of an analysis of the theoretical requirements of the typical case of organic relatedness exhibited objectively in L. J. Henderson's nomogram of the blood, (Henderson, '28) such a theory was developed for biology and stated in the atomic terms to which the predominantly chemical character of Henderson's data restricted the analysis (Northrop, '31b).

In 1928, this same theory was reached by an analysis of the theoretical requirements of the relation between space-time structure and matter in relativity physics, and formulated not merely in atomic but also in electrical and field terms (Northrop, '28).

Meantime, over a period of fifteen years, Burr had been working quite independently, with Harrison's embryological experimental technique, upon the mechanism involved in the growth and development of the nervous system, especially in Amblystoma embryos. Gradually in tracing the laying down of its neural connections, he found himself forced to describe what happens in terms of fields and waves of pattern of organization. The question arose concerning the character of this field and organic factor. Reflections and clues from the experimental findings suggested an electrical basis. Consequently, in 1930, he proposed the hypothesis, for the first time on purely technical and biological grounds, that the field and wave phenomena which his data exhibit, were to be conceived as electrical rather than purely biological in character (Burr, '32).

The two independent and different modes of attack had merged in the same conclusion.

It seemed wise, therefore, to bring the different data and reflections together in a single theory. This was published by Burr and Northrop in 1935 under the title, *The Electro-dynamic Theory of Life*. The fundamental thesis of this theory is that physical, philosophical and biological considerations warrant the extension to biology of the hypothesis that, "The pattern of organization of any biological system is established by a complex electro-dynamic field, which is in part determined by its atomic physico-chemical components and which in part determines the behavior and orientation of those components. This field is electrical in the physical sense." The paper closed with the proposal that we put to nature the questions of fact which this hypothesis raises.

These questions were three in number. First, is there a systematic steady-state electro-dynamic field in the organism which can be measured with a degree of accuracy sufficient to insure that one is getting potential differences in the organism itself and not artifacts introduced by the instrument employed? Second, when an instrument is applied to a living organism as a whole, are systematic fields in the organism as a whole, discovered? Third, what effect upon the organization as a whole of the developing organism occurs when an altered electrical field is introduced in its immediate environment?

It is the purpose of the present paper to report (1) on the findings gained to date by operational and experimental attempts to answer the first two of these questions and (2) to direct attention toward the theoretical interpretation of the findings.

THE EXPERIMENTAL APPARATUS

The theory to be tested dictated the kind of apparatus needed. Since the theory called for relatively constant electrical potential distribution and pattern in the organism as a whole, an apparatus which could pick up steady-state direct current potential differences was required. Since the aim was not to

introduce electrical effects into the organism, but to determine what electrical field characteristics the organism exhibits in its normal state, the ideal apparatus should possess (1) high input impedence, so that the minimum current is drawn from the specimen, (2) high sensitivity, (3) high stability, (4) maximum independence of external electrical disturbances, (5) direct reading in standard physical units, to remove the introduction of subjective judgments by the experimenter, (6) measurements which are independent of the flow of current, and, hence, independent of the resistance of the specimen measured, and (7) electrodes which are (a) stable and (b) in such a relation to the organism that only electrical properties in the specimen itself can affect the apparatus, while (c) also avoiding the uncertainties which direct contact of the electrodes with the organism would introduce.

The experimental side of this work has been directed and prosecuted by Burr. At the outset he consulted Professor L. W. McKeehan of the Sloane Physics Laboratory of Yale University, who immediately assigned Dr. C. T. Lane to the problem of constructing a suitable apparatus. Dr. Lane has succeeded admirably in meeting requirements one to six for an ideal apparatus, by developing a Wynn-Williams circuit, balanced in a Wheatstone bridge to a degree of stability and sensitivity rarely achieved.

The problem of the electrodes (7a above) was solved by a physical chemist, Dr. L. F. Nims, using large stable silver-silver chloride electrodes* in physiologically balanced salt solutions and (7b and c above) through the establishment of contact with the organism by means of the same salt solution in two glass micro-pipettes.

The entire apparatus (Burr, Lane, and Nims, '36) meet the ideal requirements as follows: (1) The input impedance is such that when the instrument is balanced, current drawn from the specimen is 10^{-12} part of an ampere, or in other words, practically zero. (2) The sensitivity is 10 to 100 times that of a Compton electrometer. One millimeter of deflection of a galvanometer spot is equivalent to from 1–100 micro-volts depending on the type of galvanometer employed. (3) The stability of the instrument is such that if the instrument is balanced it is still in balance after many hours of continual readings of high sensitivity. (4) The independence of external electrical disturbances is such that high shielding is not required for either the apparatus or the specimen. (5) The potential differences are read directly from the scale in terms of micro-volts and multiples thereof. (6) The measurements recorded by the apparatus are independent of the resistance of the specimen, and hence unaffected by the distance separating the micro-pipettes. Readings are also equally independent of the type of electrode used or the particular ionic constituents of the specimen. In short, there is every reason on both theoretical and operational grounds, quite apart from the methods of difference and concomitant variations also used in checking the objectivity of the readings, to suppose that any electrical potential differences discovered by the application of this apparatus to the organism, represent

* Ag-AgCl electrodes of this type were first developed by G. N. Lewis and later improved upon and much used by H. S. Harned, among others.

electrical properties of the organism as a whole and not artifacts introduced by the apparatus.

THE FINDINGS

Seven different investigations involving some 10,000 determinations have been completed by Burr and his associates (Burr and Lane, '35). In considering the results, the electro-dynamic theory of life, which has dictated the type of apparatus constructed and determined the kind of information we are trying to gain, must be kept in mind. Novel findings concerning the association of electrical properties with specific living processes have appeared previously. It was not necessary, however, to introduce the electro-dynamic theory of life, or to devise in accord with it, this particular more stable and sensitive experimental apparatus, in order to establish this fact. Since Galvani, it has been known that specific processes in living things are associated with electrical phenomena. The development of the electrocardiograph and the numerous studies on the psychogalvanic reflex bears witness to this fact. Even more explicitly the work of Mathews, Childs and Ariens Kappers attests it. The work of Adrian, Ingvar, Lund, Osterhaut, H. Davis, McCulloch and many others has amply reconfirmed this fact. Our major concern, however, is different from this. It is with the basic problem of organization in the organism as a whole, and more particularly, with the relative significance of the atomic chemical and the organic field control of its spatial pattern and temporal development that we are primarily concerned. The crucial question of fact raised by our theory is this: May it not be the case that the organism as a whole has a definite and relatively steady-state electrical field pattern of organization which can be measured and expressed in terms of potential differences objectively discoverable with the apparatus of a physicist?

Should this turn out to be the case we would have an objectively measurable, and physically and quantitatively expressible definition of biological organization which would enable us to bring certain, at the very least, of the organic characteristics of living creatures out of the purely intuitively-given qualitative realm in which biologic and holistic theories have treated them, into the same experimental and conceptual world of discourse of the physicist and chemist in which the atomic chemical constituents of living organisms are determined and formulated. Thereby, the experimental and conceptual gulf between the constituents of living things and their organization would be to a certain extent at least removed.

What are the findings? Those associated with a specific process within a living system will be indicated first.

By the mere application of the electrodes of the apparatus to the rabbit, Burr, Hill and Allen found in 1935 that the instant of ovulation, confirmed by immediate opening of the animal, exhibits itself in a sharp and marked deviation of the potential reading from the normal (Burr, Hill and Allen, '35). In 1936, Hill and Greulich repeated the same experiment with the rabbit and demonstrated it also for the cat. In 1936, Burr, G. M. Smith and Strong found

that strain differences between cancer-bearing and cancer-immune mice were accompanied by different systematic electrical field characteristics for the two strains (Burr, Smith and Strong, '36). Moreover, studies made during the major part of the life history of these mice showed definite correlations with growth, maturation and senility. They found also, by taking frequent regular readings over 12 months, on mice known to produce cancer in that time, that potential changes occur not merely at the locus of the cancer but also in the systematic potential gradient of the organism as a whole. Moreover, these changes of potential difference increase in intensity with the appearance of the cancer, and enable one to detect the inception of cancer before its presence can be determined by any other means. Burr has also found electrical concomitants of the menstrual cycle in the human female (Burr and Musselman '36). Rogers has found changes of electrical potential with the oestrous cycle of the white rat (Rogers, '36).

More interesting and important still, this association of potential changes with specific regions and processes of the organism is not a purely local phenomenon. No one would have supposed that the mere immersion of the end of a finger of each hand in a salt solution in which micro-pipettes from the apparatus are located would reflect profound local alterations in the physiology of the organism such as those involved in the menstrual cycle. Nor would one expect that two electrodes placed on the two sides of the chest would exhibit cancer development at a distance at the far end of the body from the electrodes. Yet both these effects have been found in every case examined. The local potential differences and changes of potential difference are part of a systematic potential pattern of the organism as a whole.

Independent studies of the organism as a whole have confirmed this. Burr and Hovland ('36) find potential gradients over the entire chick embryo and over the whole salamander embryo, the organism whose patterns of mitosis distribution first suggested the electro-dynamic theory of life to Burr. Furthermore, significant electrical concomitants of the early growth and development of the nervous system have been shown to exist in these forms. Finally, in both chick and salamander, potential gradients of electrical fields completely surrounding the animal have been found and measured at a distance, in the case of the salamander, of from one-quarter to one-half a millimeter from the surface of an organism, immersed in saline, $4\frac{1}{2}$ millimeters in length, these fields increasing in intensity as the micro-pipettes move up to contact with the surface of the organism. It is to be emphasized also that these potential differences define an electrical field for the organic system as a whole, and not merely for one ionic chemical component of the system. Although the electrodes used are chloride electrodes and although the ionic movements next to these metal electrodes are those of chlorine ions, the potential differences which these chlorine ionic movements record represent potential differences in the organism as a physico-chemical whole which are much more fundamental than and quite independent of the mere ionic behavior of the chlorine ions in and around the organism. It is not an electrical field for one chemical component of the organ-

ism, namely the chlorine component, but an electrical field for the physico-chemical organism as a whole which Burr's readings reveal. This is demonstrated by two experiments: (1) When the apparatus is balanced with the electrode pipettes in the salt solution, potential differences appear only with the introduction of the organism into the solution. This electrical effect is independent of the type of electrode used or the activity of any particular ion. (2) When a rod composed of two different metals pressed together is introduced into the salt solution in the place of the organism, potential differences are recorded. Since the rod contains no chlorine it is clear that the potential differences introduced by the rod must represent something more than and other than the presence of chlorine ions in the specimen. Furthermore, in all cases investigated, the potential differences are not chaotic in distribution or character, but define organized steady-state electro-dynamic fields with a systematic pattern. For example, if readings are taken between the three corners of an equilateral triangle across the trunk of an organism the voltage differences between the three points summate algebraically, as has been noted in electrocardiographic studies. It appears, therefore, that the major general thesis of the electro-dynamic theory of life is confirmed. Living organisms are complex electrical fields with a definite pattern of potential distribution as a whole.

THEORETICAL INTERPRETATION OF THE FINDINGS

One fundamental question will remain in many minds when the above conclusion is admitted. It will be asked whether the measured field is not a mere effect or secondary by-product of more fundamental changes which are purely atomic and chemical in character. Although this question is probably a vestige of the discredited absolute space-billiard ball theory of science of the nineteenth century, and hence, meaningless in terms of the particle-wave relationship of contemporary physical theory, it nevertheless deserves to be considered on its own merits in terms of the biological evidence at hand and the specific experimental technique used in obtaining it.

One point can be made at the outset. The living organisms which have been examined, whatever else they may be, are electrical fields which exhibit a definite pattern of potential distribution as a whole. This is the experimentally verified fact. The thesis that this field is a mere secondary accompaniment of more fundamental changes which are atomic and kinetic and purely chemical in character is a theory going beyond the fact. Hence, it is the person who claims that the field reduces to other categories, and not the person maintaining the electro-dynamic theory of life, who is speculating beyond that which is known by exact objective experimental methods.

On the other hand, there can be little doubt that the field is *in part* a function of the atomic physico-chemical constituents of the organism. This is suggested by the alterations in the pattern of the field shown by Burr's investigations in the case of ovulation, menstrual cycles, and cancer growth, which are known by independent purely chemical investigations to involve chemical changes.

Also, Harrison's hypothesis (Harrison, '36) concerning the role of complex molecules in determining biological symmetry points in part in this direction.

But it is an entirely different thing to say that the electrical field which Burr has measured is so completely determined by purely atomic, kinetic and non-electrical chemical factors as to be a mere by-product.* Even though Harrison's hypothesis emphasizes the dependence of biological organization upon atomic chemical factors it also involves the determination of the chemical molecules by the electrical factor since it is an essential point in Harrison's theory that the chemical molecules are oriented because of their polarity. Furthermore, to maintain the thesis that the electrical field is a by-product is not merely to go beyond Burr's experimental findings but to jump to conclusions where physico-chemical theory of the electrical properties of solutions dictates extreme caution.

PHYSICO-CHEMICAL THEORY OF THE ELECTRICAL PROPERTIES OF SOLUTIONS†

In the science of physical chemistry there has been little progress towards an adequate quantitative theory of the relation between chemical components and electrical fields in the case of solutions, although Debye, Hückel and Onsager have made important contributions in this direction. Burr's experiments reveal electrical fields of the organism *in the salt solution* surrounding the animal. Furthermore, the organism within its surface is nearer a liquid than a solid state. Hence, it is with the electrical fields of solutions that we are concerned. Since no adequate theory of the relation between atomic components and electrical fields of solutions exists at present even for inorganic systems, it is a bit premature for anyone to assert that we know what this relationship is in the case of organic systems, namely, one in which the field characteristic is a mere by-product of the motion and properties of the chemical constituents.

Moreover, Willard Gibbs, in one of the first analyses of the notion of electrochemical potentials, made an important observation bearing upon the meaning of precisely this kind of experimental investigation with electrodes which Burr and his co-workers have made. In 1899, Gibbs wrote "the consideration of the electrical potential of the electrolyte, and especially the consideration of the differences of potential in electrolyte and electrode, involve the consideration of quantities of which we have no apparent means of physical measurement, while the difference of potential in pieces of metal of the same kind attached to the electrodes is exactly one of the things which we can and do measure" (Gibbs, '28). This penetrating observation raises the question whether there is any physical meaning to the notion of the electrical potential of a single

* Recently our attention was called to a paper of A. P. Mathews ('03). In a penetrating study of "Electrical Polarity in Hydroids" he remarks (page 297), "These currents probably play a larger part in the determination of rates of growth, in the orientation or polarization of the cells, and the differentiation of the organism, in its polarity, in other words, than has been supposed."

† In what follows we are deeply indebted to the physical chemist, Dr. L. F. Nims, for calling our attention to the papers of P. B. Taylor and E. A. Guggenheim, and also for many helpful suggestions in connection with important technical and theoretical points in our analysis.

particle, since potential differences only appear when two electrodes are in junction with an electrolyte in a system of connections involving both apparatus and specimen in which there is at least one other junction. If this be the case, then the notion of potential has no meaning for a single particle but has meaning only in terms of an organic relationship of a certain kind between particles.

It is impossible to define completely the electrical field of a system as a mere by-product of the properties of its individual atomic or chemical components without any appeal to irreducible field or organic factors, unless there is meaning for the notion of electrical potential for each individual atom of the system. It would appear, therefore, that the experimental demonstration of the existence of an electrical field in living organisms necessitates the acceptance of the organic electrical field character of the organism as in part an irreducible and determining factor and not as a mere by-product of the motion and redistribution of the chemical atoms.

It has been the practice of many physical and physiological chemists to overlook this important observation by Gibbs concerning the physical meaning of electrical potentials, thereby unconsciously and uncritically carrying over to individual ions and to individual chemical atoms a concept which appears upon analysis to have meaning only in a system of physical materials. However, in 1926, experimental considerations in physical chemistry forced Harned to face this question again (Harned, '26). In 1927, Harned's pupil, Taylor, considered the matter still further (Taylor, '27), and recently E. A. Guggenheim ('30), summarizing Harned's and Taylor's analyses, has given it the most thorough analysis it has received to date. Guggenheim's conclusion is that the actual operationally-given potential $\bar{\mu}$, which he terms the electro-chemical potential, since it involves the entire system of physical relationships including the field and the atomic factors, is the only potential which has physical meaning, and that the attempt to split it up between a purely chemical potential μ, and an electro-static potential ψ is a purely arbitrary procedure which has no physical meaning and which gives rise to nothing but fictions.

This means that the electrochemical potentials given by Burr's experimental determination of living systems are not further analyzable in any way which has physical significance. Hence, the systematic electrical field in a living organism which these electro-chemical potentials define is in part at least an irreducible physical factor and not a mere by-product to be defined away in terms of the quantitative purely chemical potentials μ or the qualitative categories of the chemical constituents of living things.

Speaking in general terms, as a physical chemist, Guggenheim writes, "It has previously been realized that only these (electro-chemical potentials) . . . have *thermo-dynamic* importance, but we maintain that only they have any *physical* significance, for only they are definable in terms of physical realities." In support of this conclusion he points to the "vicious circle" exhibited "in the long realized fact that one cannot accurately determine in a solution the activity or chemical potential of an individual ion, because of the existence of liquid potential junctions whose magnitude cannot be compared without a

previous knowledge of the individual ionic activities that one wishes to measure." He adds that, "In the theory of Debye and Hückel, which treats the ions as rigid spheres . . . the specific quantities, which distinguish solutions of the same electric type, are not the diameters of the individual ion, but the distances of closest approach of the various pairs of ions." Thus the potentials which define electrical fields are not the properties of an individual ion or atom but quantities referring to the relatedness of the atoms. It is with this irreducible relatedness, not with atomicity alone, that we are confronted in the steady-state electro-dynamic field properties of living things.

Guggenheim concludes that, "It is clear that if one sets out to measure the activity or chemical potential of an individual ion the dilemma with which one is in every case confronted, is not an accident, but is the natural consequence of trying to measure a quantity which physically has no existence."

It appears, therefore, as a necessary consequence of Debye and Hückel's theory and of Gibb's observation and Harned's, P. B. Taylor's and E. A. Guggenheim's more full and recent analysis of the physical meaning of potential readings, of the type Burr has determined, that, whatever be the as yet undetermined, complete theory concerning the electrical properties of solutions, it is in the very nature of the theoretical, physical, and operational meaning of the concept of electrical potential impossible completely to define away the relatedness of the electrical field in terms of the properties of the individual chemical atoms. In other words, in the systematic potential distribution which Burr's observations have revealed there is an irreducible relational field factor.

The experimental findings, moreover, point to the same conclusion. In this connection a sharp distinction must be kept in mind between previous work on the electrical characteristics of living organisms and Burr's findings. Previous work indicated that electrical phenomena were associated with local processes or regions. Burr's work reveals steady-state direct current phenomena throughout the organism as a whole. Earlier work emphasized merely that certain local physiological processes exhibit electrical phenomena under certain circumstances. As long as this was the case, it was natural to regard the electrical as secondary to the chemical since only the chemical appeared everywhere in space and continuously in time in the organism. But now that we find the electrical factor to be a steady-state field existing continuously in space throughout the whole of the organism and persisting continuously in time (present before, continuing through, and remaining after, the local wave and energy-transfer phenomena picked up in alternating current readings), the conception of the electrical properties of living things as a secondary factor becomes less easy to maintain. The electrical field is as universally present in every process and region and stage of development of the organism as the discrete atomic chemical constituents. In short, objective experimental evidence reveals the continuous organic electrical field to be as universal a character of living systems as their atomic chemical components.

We seem justified, therefore, in concluding that the missing irreducible relational factor required to account for the organization of the physico-chemical

constituents of living things has been found in part at least, with the exact experimental apparatus and within the conceptual world of discourse of the physicist. Consequently a beginning at least seems to have been made toward bringing the constituents of living systems and their organization within the same experimental and conceptual world of discourse. The basic thesis of the electro-dynamic theory of life that living systems are complex electro-dynamic fields in part determined by their atomic constituents and in part determined by an irreducible relational factor in the field itself seems to have been confirmed by Burr's potential readings and by Gibb's, Harned's, Taylor's and Guggenheim's analyses of the physical meaning of such potential readings.

A further test of the causal efficacy of the field in determining in part the behavior of the atomic constituents will be possible when the third question of fact raised by the electro-dynamic theory of life, concerning whether changes in the normal potential distribution of the field alter the physical structure and development of the organism, can be put to nature. Plans for this experiment are in progress.

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GLUTATHIONE CONCENTRATION AND HEREDITARY SIZE

VI. COMPARATIVE POST-HATCHING STUDIES WITH BARRED PLYMOUTH ROCKS AND WHITE LEGHORNS

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INTRODUCTION

Evidence that the glutathione concentration of Barred Plymouth Rock embryos from 5 to 19 days of incubation is consistently greater than that of White Leghorn embryos of the same age was presented by Gregory, Asmundson, and Goss ('35, '36). This difference in concentration apparently is correlated with adult racial size and with a differential rate of cell proliferation that exists between breeds of large and small size as shown by Blunn and Gregory ('35). Moreover, this difference in glutathione concentration is consistent with the observations that Gregory and Goss ('33a, '33b) made on large, small, and intermediate races of rabbits and on certain hybrid combinations between large and small races. It also agrees with the results obtained in rats in which growth was induced by means of the hypophyseal growth hormone. In these cases a corresponding increase in the glutathione concentration of the muscle occurred concurrently with the stimulation of increase in body weight (Gregory and Goss, '34). In 1935 Goss and Gregory showed in new-born rabbits of the New Zealand Red Race, which breed relatively true for a certain adult size, that if growth is regulated by nursing (nutrition), the glutathione concentration of the whole carcass is correlated with nursing and with the increase in weight of the new-born rabbits.

These studies demonstrate that glutathione is correlated with growth even though the causal agents regulating growth may be quite different, such as genes for adult size (genetics), the hypophyseal growth hormone (endocrine), or the food intake (nutritional). Other glutathione relations with growth will be discussed later in this paper at the appropriate place.

Conceivably food may become a limiting factor in the egg and may be responsible to a certain extent for the characteristic type of glutathione curve found in the chicken embryo during the incubation period. We hoped that this study might give some information on this point and on the relation of food to glutathione concentration. The chief object of the study, however, was to determine the comparative glutathione values of a breed of chickens of relatively large adult size and of one breed of relatively small adult size at that period of growth when food supply is not limited by the content of the egg. For this purpose the glutathione concentration of Barred Plymouth Rock and of White Leghorn chickens was determined during the first 2 weeks of the post-hatching

period. This period includes an early post-hatching developmental stage in which the final adult weights of the breeds are not indicated by the body weights of the chickens. During the latter part of the period studied, however, the effect of breed differences in weight did become manifest.

STOCKS USED AND PLAN OF EXPERIMENT

Since the Barred Plymouth Rock and the White Leghorn stocks were the same as those used in the previous experiments ('35, '36), the adult weights need not be repeated here. The eggs from each breed were selected and paired according to their weights in the same manner as in the earlier experiments. The eggs of each breed of a series were incubated in the same incubator; and when the hatch was removed from the incubator each chick was leg-banded to preserve its individual identity. The whole incubation group that composed one series was placed in the same brooder pen. The chicks were supplied at all times with adequate water and with a standard mash used for growing baby chicks. The glutathione analysis was begun on the second day after the chicks were hatched and continued every other day through the fourteenth day. Two different batches or series of chickens were analyzed. The analysis of the first group was begun on June 14, 1936; that of the second on June 17, 1936. In making the glutathione and ascorbic acid determinations the same procedure was followed as that used in the 1936 report except that the older chickens were put through a meat grinder before being ground in a mortar with sand. The method of extraction and titration was identical with that used in the earlier experiments.

ANALYSIS OF DATA

The essential data obtained from the analysis of the Rocks and Leghorns are summarized in table 1. Series 1 represents one continuous lot of chickens the analysis of which was begun on the second day after they were hatched and was continued every other day ending with the fourteenth day, no analysis being made on the odd days such as the first, third and fifth day after hatching. Series 2, likewise, is a continuous series and was analyzed in the same manner as series 1 except that analysis was begun 3 days later. This method of organizing the experiment permitted each series to be analyzed separately or to be combined. Figure 1 presents the weights graphically in relation to age for each series separately and for the two series combined.

Series 1 will be considered first. The yolk sacs were not removed from the 2-day-old chicks of the first series, and the weights for this age are not included in the graph. The weights of both breeds were somewhat irregular. At 4 and 6 days of age the Leghorns were heavier. After this period the Rocks took the lead, which they held every day except the twelfth. At 12 days of age, due possibly to fluctuations in sampling, the Rocks weighed less than did those analyzed at 10 days of age.

The weights are complete for the second series. The Leghorns were heavier at 2 and 4 days, but by the sixth day the Rocks had forged ahead and set the

pace for the remaining periods. Some post-hatching adjustment evidently takes place between 4 and 8 days and is reflected in the weights. The growth curves of the first series, for some unaccountable reason, are much less uniform than those of the second series.

TABLE 1

A SUMMARY OF THE ESSENTIAL DATA OBTAINED FROM THE ANALYSES OF THE ROCKS AND LEGHORNS FROM TWO TO FOURTEEN DAYS OF POST-HATCHING DEVELOPMENT

Series	Age in Days	Pairs Analyzed	Rocks			Leghorns		
			Mean wt. in grams	Mean GSH Mg. %	Ascorbic Acid as GSH Mg. %	Mean wt. in grams	Mean GSH Mg. %	Ascorbic Acid as GSH Mg. %
1	2	5	35.1*	49.0	2.4	37.1*	47.0	3.0
2	2	6	32.3	48.8	5.0	33.1	46.8	4.5
					3.7			3.8
1	4	6	41.2	53.5	6.3	42.6	53.7	10.6
2	4	6	39.5	52.5	13.0	42.4	47.5	13.2
1+2	4	12	40.4	53.0	9.7	42.5	50.6	11.9
1	6	7	43.7	50.3	12.0	44.8	45.7	17.0
2	6	6	50.1	52.8	13.8	47.4	47.3	16.0
1+2	6	13	46.7	51.5	12.8	46.0	46.5	16.5
1	8	6	45.4	48.0	12.5	42.6	40.2	13.2
2	8	6	50.7	57.7	13.5	44.3	50.0	13.2
1+2	8	12	48.1	52.8	12.9	43.4	45.1	13.2
1	10	6	59.0	56.0	11.8	53.1	61.8	16.0
2	10	6	57.4	61.5	15.6	55.8	53.8	21.6
1+2	10	12	58.2	58.8	13.7	54.5	57.8	18.8
1	12	6	58.4	63.5	15.3	59.4	54.2	17.6
2	12	6	65.5	63.5	12.6	60.6	53.7	18.8
1+2	12	12	62.0	63.5	14.0	59.7	53.9	18.3
1	14	6	70.0	59.8	17.3	65.8	63.3	18.5
2	14	6	69.2	67.7	14.7	64.1	62.8	13.7
1+2	14	12	69.6	63.7	16.0	64.9	63.1	16.1

* The yolk sac was not removed in series 1 chicks at two days of age. The yolk sac was removed or had been resorbed in all the other series.

The analysis concerning the difference in weight between Rocks and Leghorns is summarized in table 2. Even though the Leghorns are heavier for the first two periods, the Rocks are consistently heavier in all ten methods of comparison; but in only two cases are the differences in weight significant but in

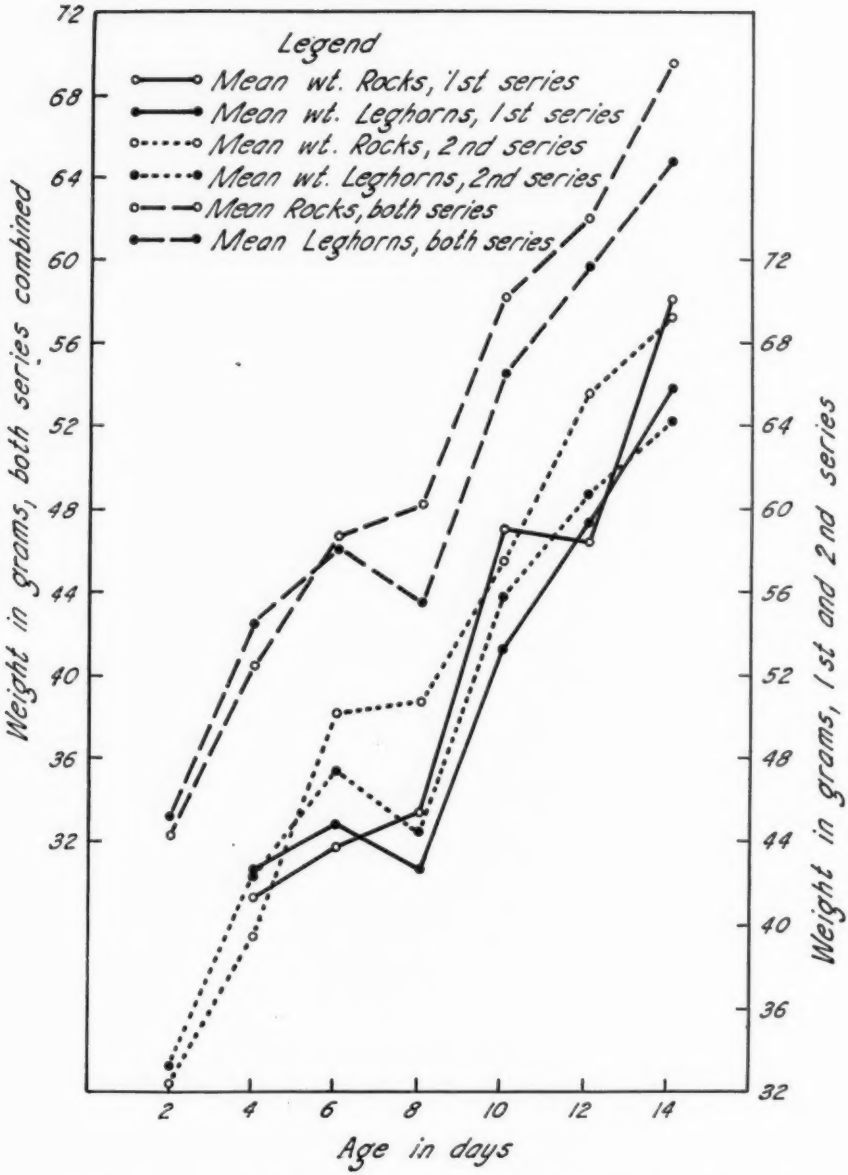

FIG. 1. Mean embryo weights in relation to age for series 1 and 2, and both series combined. Data from table 1.

several others they are approaching significance. Breed difference in weight, though manifest, is not clearly marked at this age.

GLUTATHIONE CONCENTRATION

The comparative glutathione concentrations of the two breeds for each age analyzed are presented in figure 2. These, we believe, are the first extensive glutathione data on post-hatched developing chickens that have been presented. The concentration is low at first, increases from 2 to 4 days of age, drops slightly on the sixth day, changes little on the eighth day, and may be considered to increase from then on to the fourteenth day. The concentration as well as the weights of the first series are rather irregular for both breeds.

TABLE 2

ANALYSIS OF THE SIGNIFICANCE OF WEIGHT DIFFERENCES BETWEEN ROCKS AND LEGHORNS

Type of weight comparisons between Rocks and Leghorns (Wt. in grams)	Mean Weight		t Value	t Value necessary to be significant	t Value necessary to be highly significant
	Rocks	Leghorns			
1. All chicks analyzed at 8 days of age. 12 pairs	48.1	43.5	2.454	2.718	3.106
2. All chicks analyzed at 14 days of age. 12 pairs	69.6	64.9	1.886	2.718	3.106
3. Mean for each age, both series combined. 7 pairs	52.4	50.3	1.850	3.143	3.707
4. Mean for each age, both series considered separately. 14 pairs	52.4	50.3	2.275	2.650	3.012
5. Individual pairs of all ages for first series. 37 pairs	52.7	51.2	.8534	2.326	2.576
6. Individual pairs of all ages for second series. 42 pairs	52.1	49.6	1.991	2.326	2.576
7. Individual pairs for all ages, both series. 79 pairs	52.4	50.3	2.001	2.326	2.576
8. Individual pairs for all ages except second and fourth days. First series. 31 pairs	54.9	52.9	1.053	2.457	2.750
9. Individual pairs for all ages except second and fourth days. Second series. 30 pairs	58.6	54.3	2.656	2.462	2.756
10. Individual pairs for all ages except the second and fourth days. Both series. 61 pairs	56.7	53.6	2.554	2.326	2.576

Most of this irregularity occurs on the tenth day. Here it may be observed that the Leghorns have a much greater concentration than the Rocks (first series). When the glutathione concentrations of the individual pairs at this age are considered, the Leghorn values in five out of six pairs are higher and exceed those of the Rocks with which they were paired. The point at 10 days, though obviously out of line for the Leghorns, does not seem to be out of line for the Rocks.

It should be remembered that these two series of chickens were incubated

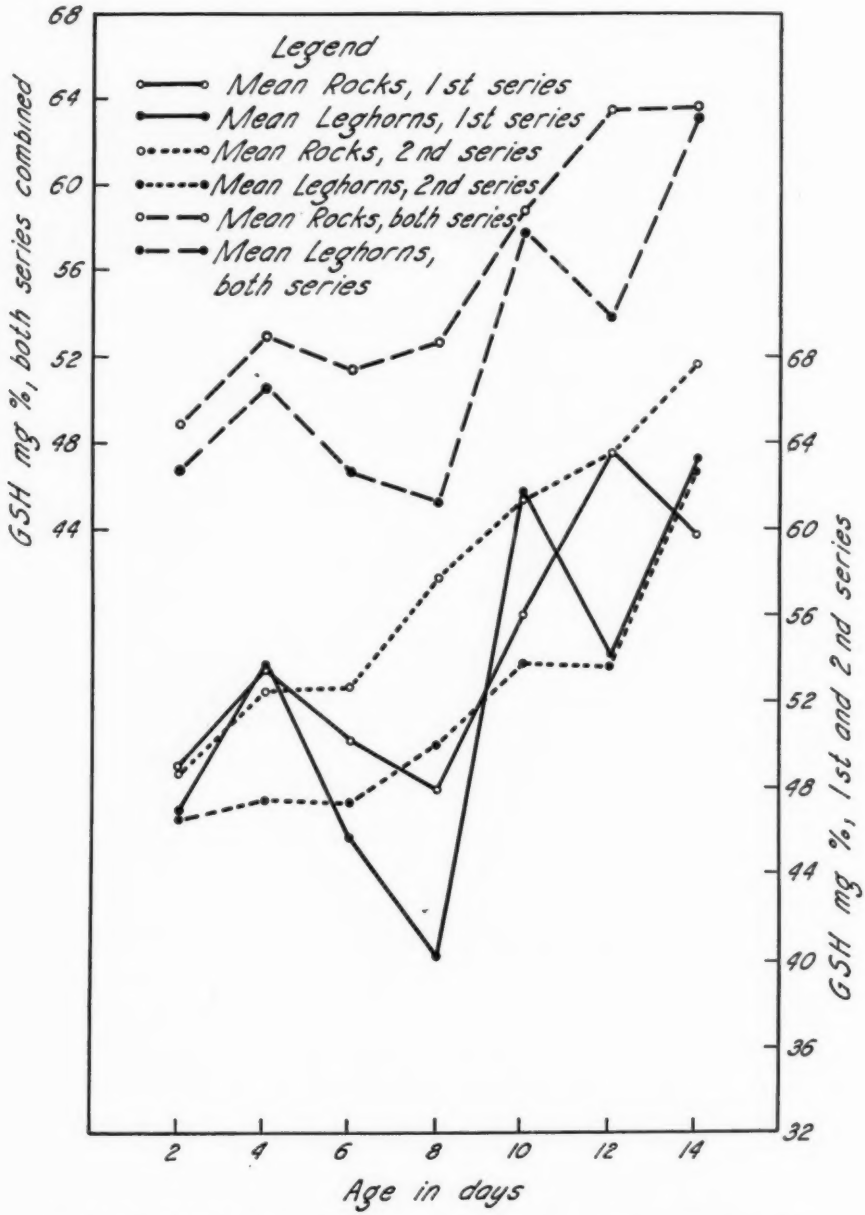

FIG. 2. Mean glutathione concentration in relation to age for series 1 and 2, and both series combined. Data from table 1.

from eggs of the same stocks and that the Rock and Leghorn chickens of each series were incubated in the same incubator. The Rock and Leghorn chickens of a series were, furthermore, kept under the same brooder and fed together. Although the two series were handled as nearly alike as possible, the difference between the series may probably be caused by an uncontrolled environmental factor or factors. When the glutathione data of the two series are combined the two curves show considerable uniformity, but the point on the Leghorn curve at 10 days seems out of line. The Rocks have a consistently higher concentration throughout the period.

Table 3 summarizes the significance of various types of glutathione comparisons between Rocks and Leghorns. Even though the Rocks are consistently higher when both series are combined, calculations were not made for each age,

TABLE 3

ANALYSIS OF THE SIGNIFICANCE OF THE DIFFERENCE IN THE GSH CONCENTRATION BETWEEN ROCKS AND LEGHORNS

Type of GSH comparisons between Rocks and Leghorns	Mean GSH concentration		t Value	t Value necessary to be significant	t Value necessary to be highly significant
	Rocks	Leghorns			
1. All chicks analyzed at 8 days of age. 12 pairs	52.8	45.1	4.118	..	3.106
2. All chicks analyzed at 12 days of age. 12 pairs	64.4	53.9	3.885	..	3.106
3. Mean for each age. Both series combined. 7 pairs	56.2	52.0	3.040	3.143	3.707
4. Mean for each age. Both series considered separately. 14 pairs	56.2	52.0	3.426	..	3.012
5. Individual pairs of all ages for first series. 42 pairs	54.3	52.2	1.394	2.326	2.576
6. Individual pairs of all ages for second series. 42 pairs	57.9	51.7	4.616	..	2.576
7. Individual pairs of all ages for birds of both series. 84 pairs	56.2	51.9	4.031	..	2.576

because, obviously the difference at certain ages is not significant. The Rocks have a significantly greater concentration at 8 and 12 days (table 3). If the two series are combined and the mean glutathione value of each age of Rocks is compared with the glutathione value for the corresponding age of Leghorns to give an n of seven, or seven pairs, the t value is 3.040. This approaches significance, (comparison 3, table 3). Comparison 4 resembles comparison 3 except that the two series are considered separately. This gives 14 pairs with a t value of 3.426, which is highly significant. Comparison 7 constitutes the individual pairs of all Rocks and Leghorns of the two series and represents the data from which comparisons 3 and 4 were obtained. Here there are 84 pairs giving a t value of 4.031, which is very highly significant. Comparison 5 represents the individual pairs of Rocks and Leghorns of the first series. Although the Rocks have a higher concentration, the t value (only 1.394) is not significant.

Comparison 6 comprises the individual pairs of series 2. The t value is 4.616, and the higher concentration of the Rocks is highly significant.

When the glutathione concentration of the Rocks is compared with that of the Leghorns of the same age, it is evident that the Rocks have a significantly greater concentration throughout the period from 2 to 14 days of post-hatching development, although the observed differences at certain ages could not be demonstrated to be statistically significant with the available data.

THE ASCORBIC ACID FRACTION

The "ascorbic acid" represents the substance of the tungstic acid filtrates extracted from the carcass that is oxidized by 2,6 dichlorophenolindophenol. For convenience, it is expressed in terms of mg. % GSH. Since this fraction is easily oxidized and is therefore rather unstable, no significance is attached to the absolute values. We were primarily interested in the glutathione concentration of the filtrates. Hence it was necessary to remove the ascorbic acid fraction with indophenol solution before final titration of the glutathione with iodine could be made. Nevertheless, since all analyses were made under uniform conditions and since the ascorbic acid value of a given filtrate could always be

TABLE 4

ANALYSIS OF THE SIGNIFICANCE OF THE DIFFERENCE IN THE ASCORBIC-ACID FRACTION BETWEEN ROCKS AND LEGHORNS

Type of Ascorbic acid comparison between Rocks and Leghorns	Mean Ascorbic acid as GSH Mg. %		t Value	t Value necessary to be significant	t Value necessary to be highly significant
	Leghorns	Rocks			
1. All chicks analyzed at 10 days. 12 pairs	18.8	13.7	2.552	2.718	3.106
2. Mean for each age. Both series considered separately. 14 pairs	14.23	11.97	3.312	2.650	3.012
3. Individual pairs for all ages. First series. 42 pairs.	14.04	11.33	2.792	2.326	2.576
4. Individual pairs for all ages. Second series. 42 pairs.	14.42	12.59	2.269	2.326	2.576
5. Individual pairs of all ages. Both series. 84 pairs.	14.23	11.97	3.617	2.326	2.576

duplicated, significance should be given these values, from a comparative standpoint. It is assumed, then, that there is a correlation between the amount found in the filtrate at the time of analysis and that present in the tissue at the time of killing. With this in mind we have presented the ascorbic acid data graphically in figure 3. It should be observed that the value is low on the second day but rises sharply by the fourth and continues to rise up to the sixth day. There is apparently a decline on the eighth day with a tendency to rise thereafter even though not all the curves agree in this respect. The curves of the first series are more uniform than those of the second. Another characteristic that should be emphasized is that in each series the concentration of the ascorbic acid fraction

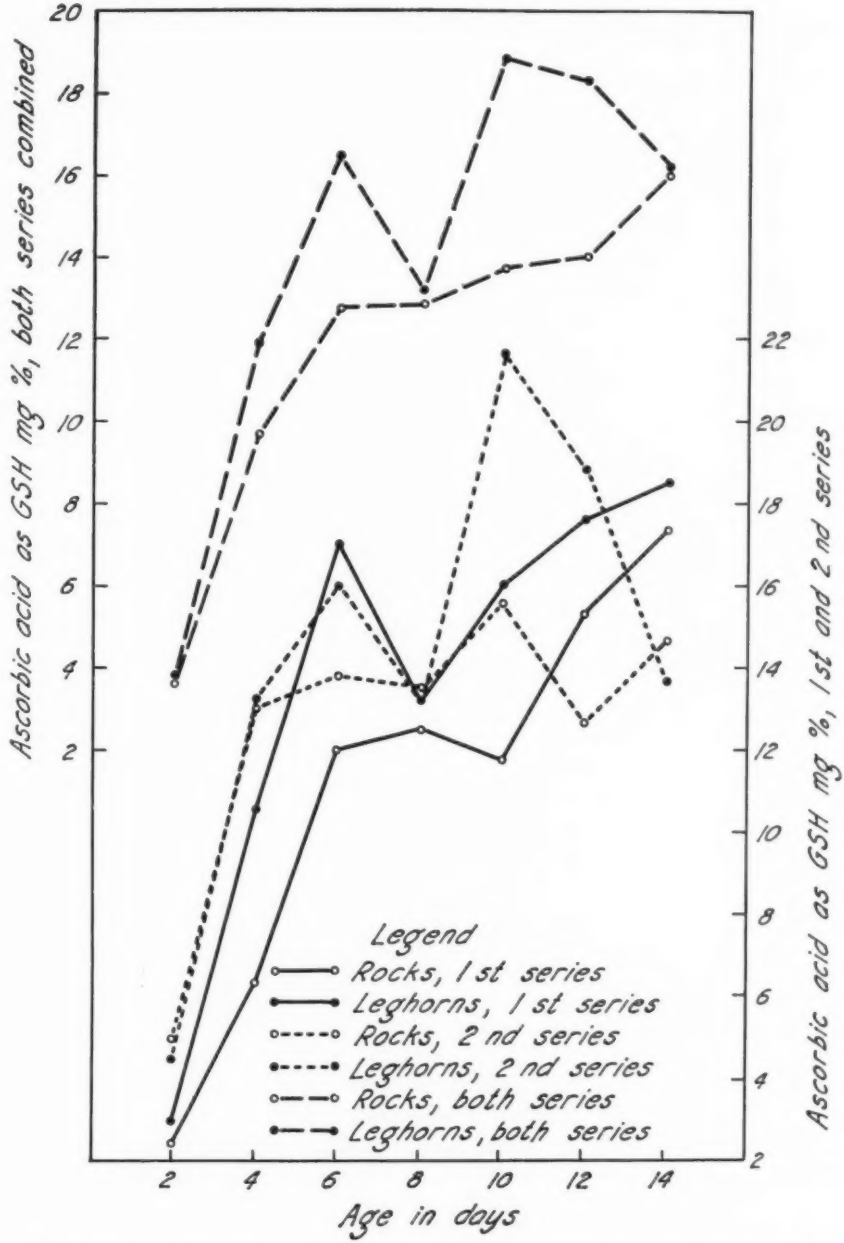
Ascorbic acid as GSH mg %, both series combined
Ascorbic acid as GSH mg %, 1st and 2nd series
Age in days
Legend
Rocks, 1st series
Leghorns, 1st series
Rocks, 2nd series
Leghorns, 2nd series
Rocks, both series
Leghorns, both series

FIG. 3. Mean ascorbic acid concentration (as GSH Mg.%) in relation to age for series 1 and 2, and both series combined. Data from table 1.

is consistently higher in the Leghorns than in the Rocks. There are no reversals (Rocks exceeding Leghorns) in the first series; but in the second series there are two slight reversals, one at 8 days and one at 14 days. When the Rocks of the two series and the Leghorns of the two series are combined, the Leghorns exceed the Rocks in concentration throughout the period.

The analyses concerning the significance of the difference in ascorbic-acid fractions between Rocks and Leghorns are summarized in table 4. The first comparison involves all the chicks analyzed at the end of 10 days. This age was selected because the maximum difference was observed at this period. The mean ascorbic acid is 18.8 for Leghorns and 13.7 for Rocks. The t value is 2.552. This approaches significance.

No other statistical comparisons were made for a definite age period because of the limited number of observations for each period. The second comparison involves the mean for each age with both series considered separately. The mean for the Leghorns is 14.23; for the Rocks, 11.97. The t value, 3.312, is highly significant. The third comparison takes into account all the individual pairs of Leghorns and Rocks of the first series. The mean value is 14.0 for the Leghorns and 11.3 for the Rocks. The t value, 2.792, is highly significant. The fourth comparison involves the individual pairs of the second series. The mean value is 14.4 for the Leghorns, 12.6 for the Rocks. The t value, 2.269, is slightly under the minimum probability of significance. The fifth comparisons includes the individual pairs of Leghorns and Rocks of all ages for both series. The mean is 14.2 for the Leghorns and 12.0 for the Rocks. The t value, 3.617, is highly significant.

When the concentrations of the ascorbic-acid fraction of Leghorns is compared with that of Rocks of the same age, it is evident that the Leghorns have a significantly higher concentration throughout the periods from 2 to 14 days of post-hatching development. No attempt is made to explain this difference but since the difference is consistent in these data and since the higher concentration is found in the smaller breed, it suggests the possibility that ascorbic acid may be involved in the problem of size inheritance and growth.

HETEROGONIC RELATIONSHIPS

1. *Glutathione and Weight.*—It has been suggested that these data which concern comparative differences in glutathione concentration between breeds in relation to hereditary size may be more adequately expressed by the logarithmic regression formula $y = bx^k$. Since Needham ('34) has discussed the problem of chemical heterogony at considerable length, further comments on applying the formula and interpreting the results are unnecessary here.

Heterogonic constants of glutathione and weight for the Rock and Leghorn post-hatching data have been calculated on a number of different bases, all of which give about the same results. One method was to consider the logarithm of the total glutathione content and the logarithm of mean weights for the different ages. A method that probably portrays the most accurate relation between glutathione and body weight is to plot the average logarithm of total

glutathione content against the average logarithm of each body-weight array with weight as the independent variate. These methods all reveal that the k value of the Rocks is slightly higher than the k value of the Leghorns; but in no case is the difference statistically significant.

Conceivably, any definite difference in k values existing between Rocks and Leghorns might be demonstrated if the observations could be increased to cover a greater range. An attempt was made to do this by adding the embryonic data of Gregory, Asmundson and Goss ('36) to the post-hatching data. Because of a sharp break in the curves of both Rock and Leghorn after the fourteenth day of incubation only the data from the fifteenth to the nineteenth days inclusive could be used. These results are plotted in figure 4. A slight break occurs in the 6.400 weight-array class for both Rocks and Leghorns in the embryo data. The same weight-array class (6.400) after 2 days of post-hatching development shows a much higher glutathione value. This break in the embryonic series might be caused by an exhaustion of certain nutrients of the egg around the nineteenth day of incubation. Apparently when the logarithm of glutathione is plotted against the logarithm of body weight or the mean weight arrays over a relatively narrow weight range, the resulting curve tends to be composed of several segments caused by slight but definite breaks in the curve. This seems apparent in both breeds. Even though the k values for the logarithms of glutathione plotted against the logarithm of body weight of two breeds are slightly and consistently different, it might be extremely difficult to demonstrate a significant difference in k values even though the Rocks have slightly greater values for most of the linear segments.

The graphic presentation of the data in figure 4 is interesting even though the results are somewhat inconclusive. Within a given weight array the mean glutathione value tends to be slightly higher for the Rocks, but it is hardly perceptible in the embryos from 15 to 19 days of incubation. On the other hand the post-hatched chickens from 2 to 14 days of age show a somewhat consistent difference in mean glutathione value for the different weight arrays. Although this is statistically significant only in the 6.600 and 6.800 weight-array classes, the trend is evident in at least two other array classes. None of the Leghorns fell into the 6.900 weight array.

2. *Ascorbic Acid and Weight.*—When the logarithm of the mean ascorbic-acid values of post-hatched chickens is plotted against the mean adult weights for the different age groups, the resulting curves for both breeds are curvilinear. If, on the other hand, the logarithm of mean ascorbic acid is plotted against the logarithm of mean weight arrays, a linear relationship may be considered to exist in both breeds. The k values of the two breeds are not significantly different.

DISCUSSION

Most of our reports in the past have considered glutathione on the basis of milligrams per hundred grams of body weight for a given age. This method of analysis has shown in all cases that breeds of greater adult weight have a significantly higher concentration when compared with breeds of lesser adult

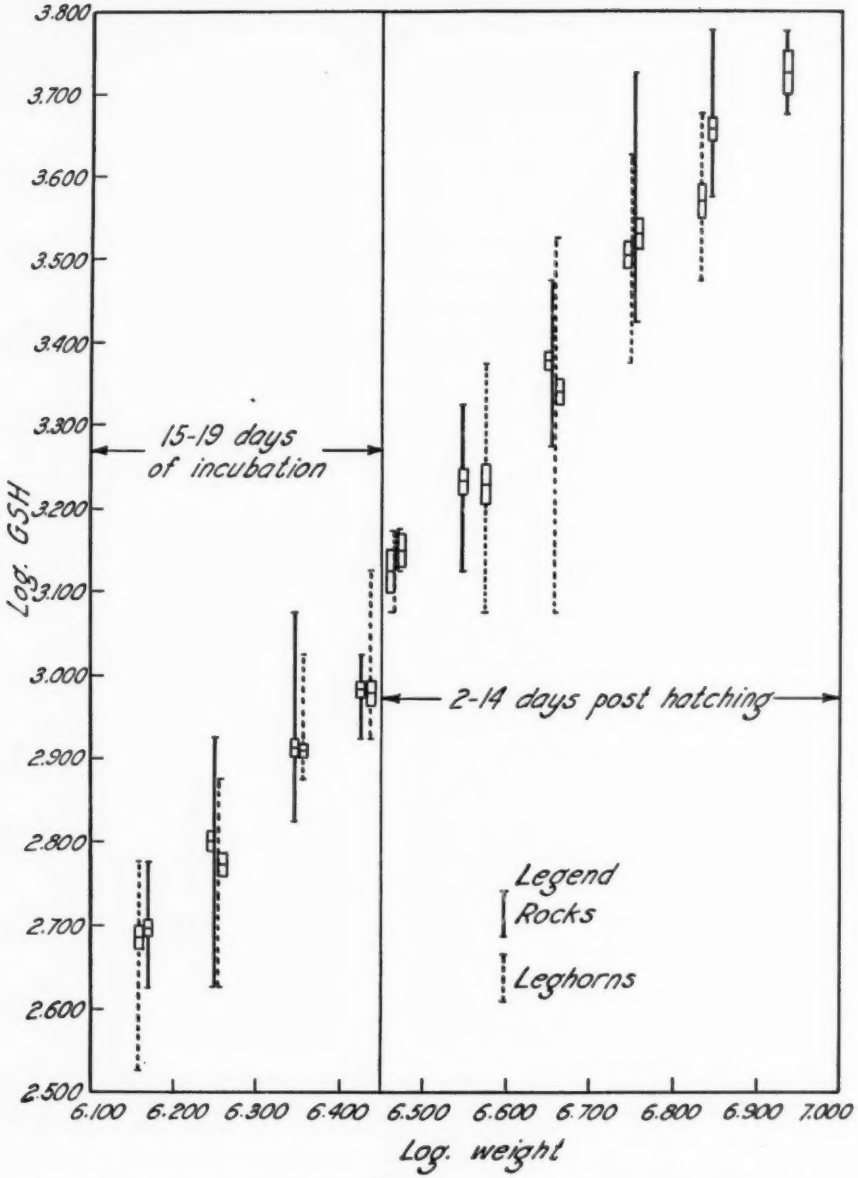

FIG. 4. Average logarithms of glutathione content plotted against average logarithm of body weight-arrays from fifteen to nineteen days of incubation and from two to fourteen days of post-hatching development for Rocks and Leghorns. The means, standard errors and range of the logarithm of glutathione values are indicated for each breed. The length of a perpendicular line represents the range of glutathione for a given mean weight-array. The middle crossbar represents the mean. The rectangles formed by the line representing the mean as a common side indicate the magnitude of the standard error. This graphic scheme of presentation is adapted from Dice and Leraas ('36).

weight at a given age. Lerner, Gregory, and Goss ('36) reanalyzed some of the earlier rabbit data published by Gregory and Goss ('33). It should be borne in mind that these data were obtained before the total iodine titration of the tungstic acid filtrates was split into ascorbic acid and glutathione fractions and also that the glutathione values include ascorbic acid. The reanalysis of the rabbit data reveals that the k value with reference to glutathione and body weight is different for some of the races. The small Polish race has a lower k value than any of the other races, and the difference is statistically significant when compared with all the other races studied. The Angora race, which is next to the Polish in size, has a greater k value than the Polish; but it is significantly lower than the k value found in races of greater adult body size. The difference between the large Flemish race and the New Zealand Red, which is somewhat intermediate to large in size, is not significant. The k values of both of these populations, however, are appreciably larger than the k values found in Angora and Polish races of lesser adult weight.

Our data presented in this paper regarding differential k values of glutathione and total body weight between Rocks and Leghorns are negative. Fragmentary indications, however, already considered under heterogonic relationships, indicate that the k value of the Rocks may be higher. One may, then, logically leave the question open in the case of the chicken, bearing in mind as the data now stand that the bulk of the evidence points to no significant difference in k value between Rocks and Leghorns. More breeds of chickens with a greater range of adult weights should be investigated during embryonic and post-hatching development. The results of an extensive study of this type should definitely settle the question of slight racial differences with respect to heterogonic relationship of glutathione and body weight.

The fact that the concentration of glutathione differs between Rock and Leghorn embryos and chicks at the same body weight indicates that irrespective of the relative rate of accretion of glutathione to the body weight (k value), the concentration of glutathione bears some relation to adult weight at early stages of development before differentiation for gross body weight has occurred.

The authors wish to express their appreciation and indebtedness to Dr. I. M. Lerner for valuable suggestions regarding the use and application of the logarithmic regression formula.

SUMMARY

1. Comparative studies of glutathione and ascorbic-acid concentration were made of the whole carcass of Barred Plymouth Rock and White Leghorn chickens from 2 to 14 days of post-hatching development. The eggs from each breed, paired for weight were incubated simultaneously in the same incubator; and the hatched chicks were placed in the same brooder pen at the same time. Two different series of Rocks and Leghorn chickens were investigated in this manner. Weights and increase in weights were also studied.

2. As shown by the analysis of weight, the Leghorns were slightly heavier at 2 and 4 days after hatching, but after 4 days of age the Rocks took the lead in

weight. The difference in weight between the breeds diverged more as the chickens grew older and was becoming significant in the later ages.

3. The comparative glutathione analyses on the basis of age clearly indicate that the Rocks, the breed of the greater adult weight, had a consistently greater concentration of glutathione than the Leghorns throughout the period from 2 to 14 days of post-hatching development. When the logarithmic regression formula is applied to glutathione and body weight the Rocks have a slightly higher k value than the Leghorns, but the difference is not statistically significant. The data presented, however, may not be sufficient to settle definitely the question of heterogony.

4. The comparative analyses of the ascorbic-acid fraction on the basis of age show that the Leghorns had a consistently higher concentration than the Rocks. When the heterogonic formula is applied to ascorbic acid and body weight, the differences in k values of the two breeds are not significant.

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